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EXPERIMENTAL STUDY IN MENINGEAL IRRITABILITY *

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Comparatively few observations are recorded on the meningeal irritability in animals. Auer [1] observed the functional effect of intraspinal injections of serums with and without preservatives in dogs and in monkeys. Flexner and Amoss [2] reported that the intraspinal injection of serum of a normal horse brings profound changes in the meningeal mechanism of the monkey.

It is evident that the substances, introduced into the subarachnoid spaces, act as foreign bodies, and, if sterile, give rise to aseptic inflammation.

The object of this investigation is to study the meningeal irritability in animals, when several substances have been introduced in the subarachnoid space. All the experiments were carried out in adult rabbits. As an index of the severity of the meningeal irritation in the rabbit, we examined the number of cells per cubic millimeter of its spinal fluid.

THE CELLULAR CONSTITUENTS OF THE NORMAL SPINAL FLUID IN THE RABBIT

The spinal fluid was taken by an atlanto-occipital puncture. In our previous papers [3] we gave the details of the method by which we were able to obtain the spinal fluid from the subarachnoid space of the rabbit. The examination of cellular constituents was made by the method of Fuchs-Rosenthal.

Twenty normal cerebrospinal fluids were examined. The results are recorded in Table 1.

As Table 1 shows, the cellular constituents in the normal cerebrospinal fluid in the rabbit are extremely scanty, averaging from about zero to ten cells per cubic millimeter, and consisting of lymphocytes. The prevailing type of cell in the fluid is the small mononuclear.

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* Received for publication, July 18, 1924.

* From the Department of Pediatrics of the Medical College, the Kyoto Imperial University.

1. Auer, J.: J. Exper. Med. **21**:43, 1915.
2. Flexner, S., and Amoss, H.: J. Exper. Med. **25**:525, 1917.
3. Kasahara, Michio: The Production of Tuberculous Meningitis in the Rabbit and the Changes in Its Cerebrospinal Fluid, Am. J. Dis. Child. **27**:428 (May) 1924.

THE EFFECT OF SIMPLE ASPIRATION ON THE MENINGEAL IRRITABILITY

At first, in order to determine the meningeal irritability due to simple aspiration of the spinal fluid, we undertook the following experiments: By an atlanto-occipital puncture 0.5 c.c. of the spinal fluid was aspirated. At intervals ranging from two, three and twenty-four hours after aspiration, we examined the number of cells in the fluid. The results are shown in Table 2.

As Table 2 shows, simple aspiration of a large quantity of the cerebrospinal fluid is not without an effect on the meninges. A transient meningeal irritation occurs.

TABLE 1.—*Results of Twenty Normal Cerebrospinal Fluids*

Rabbit	Large Lymphocytes	Small Lymphocyes	Total
1	2	2	4
2	1	1	2
3	1	3	4
4	3	1	4
5	0	0	0
6	0	2	2
7	0	2	2
8	1	2	3
9	0	2	2
10	0	3	3
11	0	0	0
12	2	5	7
13	0	0	0
14	2	1	3
15	4	6	10
16	1	1	2
17	4	4	8
18	3	2	5
19	0	1	1
20	0	2	2

THE EFFECT OF THE INTRASPINAL INJECTION OF DIFFERENT CONCENTRATIONS OF SODIUM CHLORID ON THE MENINGEAL IRRITABILITY

Rabbits were injected intraspinally with 0.5 c.c. of saline solution of various concentrations. The following concentrations of sodium chlorid were injected: from 0.1 per cent. to 0.9 per cent., inclusive, and 2.0 per cent. and 4.0 per cent. The cerebrospinal fluid was withdrawn as a rule to an extent somewhat larger than the amount to be injected. At intervals of from one to four days after the administration of the saline solutions, we examined the number of cells in the fluid. The results of these experiments are presented in Tables 3 to 11 inclusive. The fluctuation in the number of cells is graphically represented in the chart.

The experiments show very clearly the correlation between the severity of meningeal irritation and the concentration of sodium chlorid.

As the chart shows, 0.6 or 0.7 per cent. sodium chlorid solution causes the least irritation to the meninges. The stronger and the

TABLE 2.—*Cerebrospinal Fluid Examination After Two, Three and Twenty-Four Hours*

Rabbit	Body Weight, Gm.	Amount of Cerebrospinal Fluid Withdrawn, C.c.	Number of Cells per C.Mm.
1	2,390	0.5	After 2 hours 26
2	1,980	0.5	After 2 hours 30
3	1,530	0.5	After 4 hours 70
4	1,680	0.5	After 4 hours 85
5	2,100	0.5	After 24 hours 8
6	2,510	0.5	After 24 hours 5
7	1,310	0.5	After 24 hours 3

TABLE 3.—*Experiment with 0.1 Per Cent. Sodium Chlorid Solution*

Rabbit	Body Weight, Gm.	Number of Cells per C.Mm.			
		After 1 Day	After 2 Days	After 3 Days	After 4 Days
1	1,320	544	...	...	...
2	1,510	581	...	...	...
3	1,600	532	...	...	...
4	1,230	...	203	...	...
5	2,100	...	245	...	...
6	2,800	...	212	...	...
7	3,100	...	...	147	...
8	3,010	...	...	167	...
9	2,800	...	...	90	...
10	1,980	...	...	...	39
11	1,560	...	...	...	45
12	1,450	...	...	...	30

TABLE 4.—*Experiment with 0.2 Per Cent. Sodium Chlorid Solution*

Rabbit	Body Weight, Gm.	Number of Cells per C.Mm.			
		After 1 Day	After 2 Days	After 3 Days	After 4 Days
1	1,650	486	...	...	...
2	1,530	450	...	...	...
3	2,000	491	...	...	...
4	2,050	...	148	...	...
5	1,870	...	160	...	...
6	1,530	...	151	...	...
7	2,100	...	...	84	...
8	1,650	...	...	85	...
9	1,610	...	...	90	...
10	1,390	...	...	...	35
11	1,890	...	...	...	31
12	1,900	...	...	...	28

TABLE 5.—*Experiment with 0.3 Per Cent. Sodium Chlorid Solution*

Rabbit	Body Weight, Gm.	Number of Cells per C.Mm.			
		After 1 Day	After 2 Days	After 3 Days	After 4 Days
1	1,930	401	...	...	...
2	2,100	420	...	...	...
3	1,850	450	...	...	...
4	2,000	...	64	...	...
5	1,600	...	60	...	...
6	1,850	...	69	...	...
7	1,930	...	...	33	...
8	2,100	...	...	38	...
9	2,610	...	...	45	...
10	2,130	...	...	...	10
11	1,980	...	...	...	15
12	1,970	...	...	...	21

TABLE 6.—*Experiment with 0.4 Per Cent. Sodium Chlorid Solution*

Rabbit	Body Weight, Gm.	Number of Cells per C.Mm.			
		After 1 Day	After 2 Days	After 3 Days	After 4 Days
1	2,300	450	...	...	...
2	2,000	400	...	...	...
3	1,980	412	...	...	...
4	1,780	...	51	...	...
5	1,960	...	43	...	...
6	1,670	...	90	...	...
7	2,100	...	...	38	...
8	2,050	...	...	39	...
9	1,830	...	...	49	...
10	1,710	...	...	...	5
11	1,680	...	...	...	8
12	1,920	...	...	...	7

TABLE 7.—*Experiment with 0.5 Per Cent. Sodium Chlorid Solution*

Rabbit	Body Weight, Gm.	Number of Cells per C.Mm.			
		After 1 Day	After 2 Days	After 3 Days	After 4 Days
1	2,000	150	...	...	...
2	1,980	160	...	...	...
3	1,780	170	...	...	...
4	1,900	...	72	...	...
5	1,850	...	79	...	...
6	2,100	...	70	...	...
7	2,200	...	...	39	...
7	2,200	...	...	39	...
8	2,050	...	...	35	...
9	2,110	...	...	38	...
10	1,960	...	...	...	4
11	1,900	...	...	...	5
12	2,100	...	...	...	6

TABLE 8.—*Experiment with 0.6 Per Cent. Sodium Chlorid Solution*

Rabbit	Body Weight, Gm.	Number of Cells per C.Mm.			
		After 1 Day	After 2 Days	After 3 Days	After 4 Days
1	2,300	140	...	...	...
2	2,190	138	...	...	...
3	1,850	142	...	...	...
4	2,300	...	47	...	...
5	2,020	...	50	...	...
6	2,060	...	51	...	...
7	2,080	...	...	39	...
8	1,960	...	...	29	...
9	1,900	...	...	20	...
10	1,910	...	...	...	10
11	2,070	...	...	...	2
12	2,110	...	...	...	8

TABLE 9.—*Experiment with 0.7 Per Cent. Sodium Chlorid Solution*

Rabbit	Body Weight, Gm.	Number of Cells per C.Mm.			
		After 1 Day	After 2 Days	After 3 Days	After 4 Days
1	2,500	157	...	...	...
2	2,250	148	...	...	...
3	2,090	160	...	...	...
4	2,300	...	50	...	...
5	2,000	...	59	...	...
6	2,190	...	56	...	...
7	1,980	...	...	24	...
8	1,960	...	...	30	...
9	1,830	...	...	25	...
10	1,900	...	...	...	9
11	1,890	...	...	...	8
12	1,790	...	...	...	3

TABLE 10.—*Experiment with 0.8 Per Cent. Sodium Chlorid Solution*

Rabbit	Body Weight, Gm.	Number of Cells per C.Mm.			
		After 1 Day	After 2 Days	After 3 Days	After 4 Days
1	2,000	204	...	...	...
2	2,020	215	...	...	...
3	1,600	225	...	...	...
4	1,980	...	78	...	...
5	2,300	...	78	...	...
6	2,070	...	68	...	...
7	2,100	...	...	43	...
8	1,790	...	...	48	...
9	2,000	...	...	41	...
10	2,010	...	...	...	3
11	2,030	...	...	...	5
12	1,990	...	...	...	8

TABLE 11.—*Experiment with 0.9 Per Cent. Sodium Chlorid Solution*

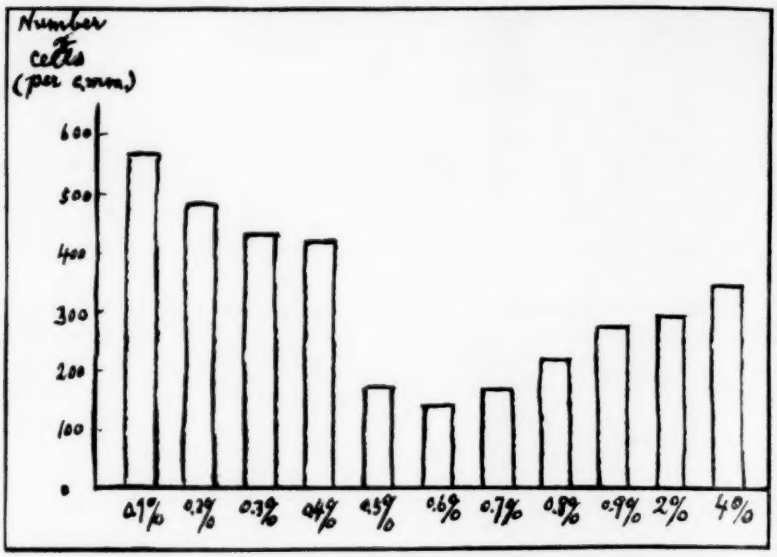
Rabbit	Body Weight, Gm.	Number of Cells per C.Mm.			
		After 1 Day	After 2 Days	After 3 Days	After 4 Days
1	2,220	209	...	...	...
2	2,180	286	...	...	...
3	2,000	290	...	...	...
4	2,050	...	100	...	...
5	2,030	...	96	...	...
6	2,090	...	120	...	...
7	2,160	...	...	57	...
8	2,090	...	...	60	...
9	2,100	...	...	50	...
10	2,230	...	...	...	9
11	1,990	...	...	...	9
12	2,010	...	...	...	8

TABLE 12.—*Experiment with 2.0 Per Cent. Sodium Chlorid Solution*

Rabbit	Body Weight, Gm.	Number of Cells per C.Mm.			
		After 1 Day	After 2 Days	After 3 Days	After 4 Days
1	2,110	258	...	...	...
2	1,930	296	...	...	...
3	2,060	278	...	...	...
4	1,820	...	112	...	...
5	1,631	...	99	...	...
6	2,100	...	100	...	...
7	1,930	...	...	56	...
8	2,090	...	...	39	...
9	2,000	...	...	48	...
10	1,670	...	...	...	12
11	1,590	...	...	...	15
12	1,920	...	...	...	18

TABLE 13.—*Experiment with 4.0 Per Cent. Sodium Chlorid Solution*

Rabbit	Body Weight, Gm.	Number of Cells per C.Mm.			
		After 1 Day	After 2 Days	After 3 Days	After 4 Days
1	2,100	354	...	...	...
2	1,980	368	...	...	...
3	1,730	302	...	...	...
4	2,000	...	174	...	...
5	2,050	...	147	...	...
6	1,890	...	120	...	...
7	1,930	...	...	39	...
8	1,910	...	...	48	...
9	2,010	...	...	59	...
10	2,000	...	...	...	16
11	2,010	...	...	...	13
12	1,980	...	...	...	12



The effect of the intraspinal injection of different concentrations of sodium chlorid on the number of cells in the cerebrospinal fluid.

TABLE 14.—*Experiment with Ringer's Solution*

Rabbit	Body Weight, Gm.	0.7% NaCl Solution	Ringer's Solution	No. of Cells per C.Mm. After 1 Day	No. of Cells per C.Mm. After 2 Days
1	2,380	0.5 c.c.	.....	142	51
2	2,190	0.5 c.c.	.....	151	56
3	2,310	0.5 c.c.	.....	158	49
4	1,960	.....	0.5 c.c.	110	37
5	1,890	.....	0.5 c.c.	93	29
6	2,000	.....	0.5 c.c.	90	30

TABLE 15.—*Number of Cells After One and Two Days*

Rabbit	Body Weight, Gm.	No. of Cells per C.Mm. After 1 Day	No. of Cells per C.Mm. After 2 Days
1	1,970	102	...
2	1,730	90	...
3	1,850	95	...
4	2,000	85	...
5	2,100	79	...
6	2,010	...	52
7	1,890	...	40
8	1,790	...	48
9	1,900	...	30
10	1,910	...	35

weaker concentrations produce more intense irritation. The amount of sodium chlorid in the normal spinal fluid in the rabbit averages about from 0.62 to 0.7 per cent. Therefore, we may say that 0.6 or 0.7 per cent. saline solution seems to give an osmotic pressure equal to the cerebrospinal fluid in the rabbit.

THE EFFECT OF RINGER'S SOLUTION AND 0.7 PER CENT. SODIUM CHLORID SOLUTION ON MENINGEAL IRRITABILITY

Halliburton [4] suggested from the chemical point of view, that Ringer's solution is the liquid most similar to the cerebrospinal fluid.

In order to compare the effect of Ringer's solution and 0.7 per cent. sodium chlorid solution on meningeal irritability, we carried out the following experiments:

After the withdrawal of 0.5 c.c. of the cerebrospinal fluid, rabbits were injected intraspinally with 0.5 c.c. of 0.7 per cent. sodium chlorid

TABLE 16.—*The Effect of Serum on Meningeal Irritability*

Rabbit	Body Weight, Gm.	Intraspinal Injection, 0.2 C.c.	Number of Cells per C.Mm. After 1 Day	After 2 Days	After 3 Days	After 4 Days
1	1,890	Fresh serum of rabbit.....	737	158	72	23
2	1,830	Fresh serum of rabbit.....	805	143	79	35
3	1,850	Fresh serum of rabbit.....	763	143	90	25
4	1,900	Inactive serum of rabbit....	119	50	13	10
5	2,000	Inactive serum of rabbit....	130	62	21	9
6	2,030	Inactive serum of rabbit....	141	73	30	15
7	2,010	Fresh serum of goat.....	1,067	222	..	22
8	1,900	Fresh serum of goat.....	1,235	261	..	28
9	1,890	Fresh serum of goat.....	1,025	200	..	16
10	1,960	Inactive serum of goat.....	191	77	..	12
11	1,980	Inactive serum of goat.....	139	100	..	15
12	2,000	Inactive serum of goat.....	161	73	..	9

solution or Ringer's solution (0.7 per cent. sodium chlorid + 0.02 per cent. potassium chlorid + 0.02 per cent. calcium chlorid).

One or two days later the cerebrospinal fluid was withdrawn and an examination of the cellular constituents was made. The results are shown in Table 12.

Table 12 shows that Ringer's solution causes less irritation to the meninges, than the 0.7 per cent. saline solution.

THE EFFECT OF HUMAN CEREBROSPINAL FLUID ON MENINGEAL IRRITABILITY IN THE RABBIT

After the withdrawal of 0.5 c.c. of the spinal fluid, rabbits were injected intraspinally with 0.5 c.c. of normal human cerebrospinal fluid.

The examination of the cellular constituents was made one or two days after injection. The results are given in Tables 13, 14 and 15.

Tables 13, 14 and 15 show that the introduction of human cerebrospinal fluid into the subarachnoid space of the rabbit causes the least irritation to the meninges.

4. Halliburton, W.: Brit. M. J. **2**:609 (Nov. 4) 1916.

THE EFFECT OF SERUM ON MENINGEAL IRRITABILITY

Rabbits were injected intraspinally with a homologous or heterogeneous serum. The amount of the serum injected was 0.5 c.c. Before the intraspinal injection a rather large amount of the spinal fluid was withdrawn.

The results are given in Table 16.

Table 16 shows that the severity of meningeal irritability is less with homologous than with heterogeneous serum. Fresh serum acts as a severe irritant to the meninges.

The results are in harmony with those of Flexner and Amoss.

CONCLUSIONS

An examination of the experimental evidence of the preceding pages would appear to have established the following facts:

1. Simple aspiration of a large quantity of the spinal fluid produces a transient irritation in the meninges.
2. Ringer's solution is a liquid similar to the cerebrospinal fluid.
3. A solution isotonic to the cerebrospinal fluid of the rabbit is between 0.6 and 0.7 per cent. sodium chlorid.
4. The severity of meningeal irritation is less with homologous than with heterogeneous serum. Fresh serum acts as a severe irritant to the meninges.

THE PROTECTIVE POWER OF INFANTS' AND MATERNAL SERUM AGAINST PNEUMOCOCCI *

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This study was undertaken to determine whether there is, in infancy, an immunity to the fixed types of pneumococci. The results we believed might help to explain why bronchopneumonia is relatively frequent and lobar pneumonia relatively infrequent during the first years of life.

The possible reasons why bronchopneumonia is the most common type in infants, in debilitated children and those suffering from certain other infections, while lobar pneumonia selects as its victims older children in good physical condition, has long been of interest to us. Various theories have been advanced but none seem to have offered sufficient evidence for confirmation. The fact that pneumococci are practically always the cause of the lobar type, while other organisms either alone or associated with pneumococci have been isolated in cases of bronchopneumonia, suggested the possibility that infants may have an immunity to pneumococcic infections. The immunity of infants to certain other infections such as measles and diphtheria lends support to this idea.

REVIEW OF THE LITERATURE

Lamar and Meltzer,[1] in 1912, were able to produce lobar pneumonia by intratracheal insufflation of pneumococci in dogs. Wollstein and Meltzer [2] produced bronchopneumonia by the same method, using streptococci and influenza bacilli. This work has been confirmed and further elaborated on by Blake and Cecil,[3] who employed monkeys as subjects instead of dogs.

Comparatively little has been published on the bacteriology of the pneumonias of infancy, and until better methods are introduced this work will be open to some criticism. Satisfactory specimens of sputum are difficult to obtain and are nearly always badly contaminated by the flora of the upper respiratory tract. The use of mice for the isolation

* Received for publication, June 16, 1914.
* Read before the Thirty-Sixth Annual Meeting of the American Pediatric Society, Pittsfield, Mass., June 5-7, 1924.
* From the Department of Pediatrics of Western Reserve University and Lakeside Hospital.

1. Lamar and Meltzer: J. Exper. Med. **15**:133, 1912.
2. Wollstein and Meltzer: J. Exper. Med. **16**:126, 1912; ibid. **18**:548, 1913.
3. Blake, F. G., and Cecil, R. L.: J. Exper. Med. **31**:445 (April) 1920, and a series of papers appearing in the same journal following this.

of bacteria may lead one astray because of the selective action of the pneumococcus for this animal. As the mouse is highly susceptible to the pneumococci, a few of these organisms may readily outgrow a larger number of other bacteria. Even necropsy studies may not be conclusive because of a premortal invasion of organisms from higher up in the respiratory tract. A great variety of bacteria are usually found in bronchopneumonic lungs at necropsy.

Wollstein and Benson,[4] in thirty-four cases of bronchopneumonia, found the Type I pneumococcus three times, Type II four times and Type IV twenty-one times. Other organisms were encountered on six occasions. Lyon,[5] in forty-one cases of bronchopneumonia, found the three fixed types (Types I, II and III) seven times, in three of which they were associated with other organisms. Type IV was found nineteen times, in ten of which it was accompanied by other bacteria. In fifteen cases no pneumococci were identified.

The findings of the work of Pisek and Pease[6] are similar to the results found in the foregoing. In their conclusions is found the following statement: "The infection which is the etiologic factor of lobar pneumonia is always the pneumococcus, while a bronchopneumonia may be due to a number of organisms such as the streptococcus, or influenza bacillus, occurring alone or as a mixed infection. If pneumococci are present in bronchopneumonia they are usually one of a group of organisms, or at least of low virulence and resemble the organisms frequently found in the mouth."

We chose the protective power of the serum as being the most valuable means of demonstrating an immunity. Agglutinins and precipitins are not always an index to the immunity of the person and the methods for their demonstration, particularly when present in small amounts, are more subject to errors due to the personal equation.

Clough[7] has shown that a considerable number of normal adults have in their serum protective power against the fixed types of pneumococci. Among twenty normal adults, he found that in doses of 0.2 c.c. of serum, 20 per cent. protected against Type I and 40 per cent. against Types II and III. This protection varied from ten to one hundred thousand minimum lethal doses of the pneumococci. He did not determine the nature of this protection, being unable to demonstrate agglutinins, precipitins, bacteriotropins or bacteriolysins.

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4. Wollstein, Martha, and Benson, A. W.: Types of Pneumococci Found in the Pneumonias of Infants and Young Children, Am. J. Dis. Child. **12**:254 (Sept.) 1916.

5. Lyon, A. B.: Bacteriologic Studies of One Hundred and Sixty-Five Cases of Pneumonia and Postpneumonic Empyema in Infants and Children, Am. J. Dis. Child. **23**:72 (Jan.) 1922.

6. Pisek and Pease: Am. J. M. Sc. **151**:14, 1916.

7. Clough, P. W.: Southern M. J. **12**:360 (July) 1919.

The specimens of blood for this work were all obtained at the time of delivery. Those designated as infants' serums were taken from the umbilical cord, and the maternal blood was taken from the antecubital vein.

Cultures of pneumococci, Types I, II and III were furnished us by the New York City Board of Health. They were passed through a series of white mice to raise the virulence and then the minimum lethal dosage was determined. The serums were injected intraperitoneally in amounts varying from 0.4 c.c. to 1 c.c. In the latter part of the study 0.5 c.c. was regularly employed. The pneumococci were injected in the same manner, suspended in 1 c.c. of a normal saline solution. The injection of the serum preceded that of the bacteria by twenty-four hours. As controls, mice to the number of two-thirds of those having serum were injected with each type of pneumococci. For example, if twelve serums were injected at one time, thirty-six mice were required for the three types and eight as controls for each type, making a total

Cultures of Pneumococci, Types I, II and III

	Number of Serums	Number of Mice Protected	Per Cent. Protected
Type I Pneumococcus. 145 Serums:			
Infants'	79	26	33.0
Mothers'	66	26	40.9
Type II Pneumococcus. 119 Serums:			
Infants'	67	21	31.3
Mothers'	52	22	42.3
Type III Pneumococcus. 135 Serums:			
Infants'	74	21	28.3
Mothers'	61	25	40.9

of sixty mice. These controls were always employed, even though the minimum lethal dose had been constant for several months. If any of the controls lived the results for that experiment were rejected.

The results of this work are summarized in the table.

COMMENT

No attempt was made to determine the amount or the nature of this protection.

The serums obtained from the umbilical cords were not, as a rule, in as good condition as those from the mothers' veins. Frequently a slight degree of hemolysis was present. This might account for the discrepancy in the protective power of the two groups.

In seventeen instances both the mother and her baby showed protection against the same organism. There then remained a considerable number in which only one showed this property. Sometimes this was the mother and sometimes it was the infant. The familial character of this protection has not been demonstrated to be as constant as one might suppose. This brings up the question as to whether the controls should

not have been injected with some substance, analogous to serum, but known to have no protective power. We tried inactivated serum and found that it still retained its protective power. The serum from almost any animal might have the same property as the human serum. A foreign protein or an inert substance might render the peritoneum more susceptible to infection. For these reasons no control substance was used.

Since the three groups of pneumococci are generally believed to be closely related and since this protective power might be nonspecific, a serum protecting against one type should protect against all three types. This was the case in only eight instances, five mothers and three infants. Clough, using adults' serums, records the same findings, none protecting against the three types. He and other writers have shown that the immunity following lobar pneumonia is absolutely specific for the homologous types.

CONCLUSIONS

Approximately 40 per cent. of parturient mothers' serums showed a protective power against the three fixed types of pneumococci.

This protective power was present in about 30 per cent. of the serums taken from the umbilical cord.

The theory that the low incidence of lobar pneumonia during infancy is due to an immunity for the fixed types of pneumococci cannot be substantiated by these results.

THE BASAL METABOLISM OF CHILDREN WITH IDIOPATHIC EPILEPSY *

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Studies on the blood and urine chemistry, the basal metabolism and the effect of symptomatic measures on children with idiopathic epilepsy have been made in this clinic during the last four years.

In view of the fact that varying reports have appeared in the literature from time to time on the use of thyroid in epilepsy, studies of the basal metabolism of eleven epileptic children were made. These patients were all of normal physical development and had not undergone treatment with thyroid extract. In the majority of instances they were of normal weight and height for age, and with the exception of Case 3, which patient was taller than the average and about 25 per cent. underweight, and Case 11, which patient was slightly underweight, while Cases 5 and 6 were more than 10 per cent. above the average weight for age.

The results of the determinations of the basal metabolism in this series is presented in the accompanying table.

The metabolism was normal or elevated in all instances.[1] The high metabolism found in Case 3 may be partially due to the fact that the patient was considerably underweight, falling in the class of malnutrition in which the total heat production is greater than that of normal children of the same weight. These findings are consistent with those of Boothby,[2] who found that in 79 per cent. of twenty-four cases studied the metabolism was high or normal.

Observations on Case 5, during an attack of grand mal, in which the activity was great during most of a thirty minute period, showed an increase of 43 per cent. over the results of the previous day. Determinations made on Case 7 while having attacks of petit mal showed no

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* From Children's Medical Department, Massachusetts General Hospital.
* This paper is No. 34 of a series of studies in metabolism from the Harvard Medical School and allied hospitals. The expenses of this investigation have been defrayed, in part, by a grant from the Proctor Fund of the Harvard Medical School for the study of chronic diseases.

1. Talbot, F. B.: Standards of Basal Metabolism in Normal Infants and Children, Am. J. Dis. Child. **21**:519 (June) 1921.

2. Boothby, W. M., and Sandiford, Irene: Basal Metabolism, Physiol. Rev. **4**:69 (Jan.) 1924.

The Basal Metabolism of Eleven Children With Idiopathic Epilepsy

Case	Age, Years	Sex*	Weight, Kg.	Height, Cm.	Respiratory Quotient	Heat Production 24 Hours: Total Calories	Normal Standards: Total Calories for: Weight	Normal Standards: Total Calories for: Height	Pulse	Activity	Temperature
1	10	♀	27.67	134.5	0.84	1,097	970	1,010	..	I	98.2-97.7
2	9½	♀	29.65	136.9	0.74	1,105	1,020	1,040	..	II	.....
3	12	♂	25.09	146.0	0.80	1,453	1,000	1,230	80	II	99.3-97.0
4	7½	♀	20.71	.....	†	1,075	825	.....	..	II	.....
5	10	♂	31.36	.....	0.80	1,326‡	1,140	.....	..	I+	.....
6	9	♀	30.85	.....	0.79	1,238	1,065	.....	..	II	.....
7	8½	♀	27.92	137.0	0.82	1,190‡	900	1,040	81	I	98.7
	8½	..	27.20	137.5	0.77	1,159‡	975	1,040	81	I	99.4
8	11	♂	28.29	134.6	0.82	1,192‡	1,090	1,120	64	I+	97.7
	11½	..	31.36	135.7	0.76	1,424	1,140	1,125	83	I+	98.4
9	13	♂	37.73	138.0	0.87	1,305‡	1,280	1,150	75	I+	....
10	11½	♀	32.35	136.1	0.79	1,382‡	1,100	1,025	109§	I+	99.0
			32.06	136.1	0.79	1,306‡	1,098	1,025	85	I+	....
11	13½	♂	30.05	142.6	0.87	1,052‡	1,120	1,200	95	I	99.0
			29.95	.....	0.85	1,054‡	1,110	.....	87	I	97.0

* In this column, ♀ indicates female; ♂, male.
† Computed on quotient 0.83.
‡ Average of two periods.
§ Nervous on morning of metabolism.

appreciable increase. It was noted that during the time the metabolism study was made the patient had attacks of unconsciousness without any muscular convulsions visible to the eye. Bornstein [3] found in his observations a markedly increased metabolism after an epileptiform attack, remaining so for a period of twenty-four hours. This was not studied in detail in our cases but no evidence was obtained to support this result.

COMMENT

The basal metabolism of this series of children with idiopathic epilepsy was normal or elevated. This is interpreted to mean that thyroid gland medication is not indicated in the treatment of idiopathic epilepsy in childhood.

3. Bornstein: Monatschr. f. Psychiat. u. Neurol. **25**:392, 1908.

THE VALUE OF THE BANANA IN THE TREATMENT OF CELIAC DISEASE*

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Some years ago I treated a child, aged 3 years, who suffered from a severe case of anorexia nervosa. She had reached a serious state of depletion and weakness from her self imposed starvation, refusing all food and regurgitating that fed to her by gavage. She finally accepted a banana, with the result that other food was taken in a more or less normal amount within forty-eight hours. There was a complete relapse when the banana was withheld, and food was taken normally only with bananas.

This experiment was repeated to test the validity of the observation, always with the same result, until a time came when her appetite was normal whether bananas were included in the diet or not. The action was such as is attributed to a hormone. It was natural, therefore, to test bananas in a case of celiac disease where anorexia was a prominent symptom.

Celiac disease is probably the most troublesome disturbance of nutrition of late infancy and early childhood. The consensus of opinion is that it is a functional disease characterized by inability to utilize properly carbohydrates and fats. To what extent the carbohydrate or the fat is at fault is not quite so clear. Herter,[1] who studied these cases from a laboratory standpoint probably more carefully than any one else, found intolerance of carbohydrates to be the most important feature, resulting in the deprivation of the organism of the foodstuff on which it mainly depends for its caloric needs, and stated that: "In the severest forms of 'Infantilism' the total quantity of carbohydrates which can be tolerated may be very small, and it may be possible to supply in this form less than one-fifth of the calories required by the organism instead of nearly one-half as in health. The fats are, on the whole, better tolerated than the carbohydrates." The difficulty in treating these cases is proverbial, relapses even after marked temporary progress being the regular experience. Ten cases are reported here; eight of the patients were clinically cured by the form of therapy described below. The two patients not treated died.

TREATMENT

The treatment of this condition has always been troublesome. Up to the present time there has been no method reported which has been

* Received for publication, June 25, 1924.

1. Herter, C. A.: Infantilism from Chronic Intestinal Infection, New York, The Macmillan Company, 1908.

consistently successful. One of the striking peculiarities of this disease is that now and again some treatment is instituted for a patient which leads to a remarkable improvement resulting in a complete cure, yet when the same method is applied to an apparently parallel case it results in failure.

The treatment may be divided into two parts: (1) Keeping the gastro-intestinal tract as free from toxic accumulations as possible. This is best accomplished by a full dose (15 gm.) of castor oil once each week, and irrigation of the colon daily with as many liters of bicarbonate of soda solution (15 gm. to a liter of warm water) as may be necessary to obtain a clear return.

(2) Dietetic. Plain milk should not be given; the most satisfactory substitute is protein (albumin) milk. In several cases protein milk prepared with calcium caseinate was accepted after protein milk prepared in the usual way had been refused. Lactic acid milk may be used in some cases. Dry milk, especially such as has been prepared with a fat free milk, is sometimes tolerated. Unsweetened and rarely sweetened condensed milk may be used successfully. Pot cheese prepared from whole milk is usually as well borne as when it is prepared from skimmed milk. Broths may be used; white of eggs may also be used. Gelatin is refused by some children, but when taken seems especially desired. After improvement has set in, meat is often well borne. The above constitutes the list of foods from which the protein ration is selected.

Carbohydrates should be vigorously avoided except as they occur in the before mentioned milk products. Saccharin should be used for all sweetening. Bread, crackers, potatoes and cereals may not be used. In extreme cases every trace of sugar except as it may occur in protein milk prepared according to Finkelstein's formula or in pot cheese, must be eliminated before success in treatment is attained.

There is one exception, i. e., sucrose as it occurs in the extremely ripe banana. This is tolerated perfectly, and herein lies the crux of the entire matter. Heretofore it has been impossible in the severe cases to give any carbohydrate without damage, whereas banana is not only well tolerated, but rapidly changes the entire picture of the disease to one of well being.

An under-ripe banana is a starch, an over-ripe banana is a sucrose with an invert sugar,[2] and like most sugars easily assimilated. The banana has been the victim of one of those curious antagonisms so frequent in medicine, which made it difficult of acceptance by lay people, as a suitable infant food, although in the tropics it has been so used for generations.

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2. Pease, M. C., and Rose, A. R.: Banana as a Food for Children, Am. J. Dis. Child. **14**:379 (Nov.) 1917.

Of interest in connection with the present paper is the statement that in Porto Rico the town dwellers who eat much bread suffer from sprue, the farmers who live largely on bananas never.[3]

A ripe banana usually has a brown skin, or brown mottling. It must have a bland sweet taste, not acrid, and should never pucker the mouth. The number of bananas offered to a child may be quickly increased by one or two daily until the patient's demand for carbohydrate is satisfied. In the earlier cases only a small quantity was used, and the number increased slowly. With added experience this was found to be unnecessary, and rapid increase in number was made so that in a recent case an infant, aged 24 months, took sixteen bananas daily, a short time after they had been prescribed. The anorexia in some cases is so extreme that even banana is refused at the beginning, only protein milk being acceptable. Sooner or later the banana is relished. Then it is to be increased to the maximum which the child will take, usually from four to eight daily.

TABLE 1.—*The Typical Diet*

	Amount, Ounces	Protein, Gm.	Carbohydrate, Gm.	Fat, Gm.	Calories
Albumin milk	40	36	20	30	500
Pot cheese (milk 16 oz.)	..	20	5	17½	250
Banana	6	6	90	3	410
Orange	1	..	10	..	40
Vegetables	2	1	2	..	10
Gelatin	⅓	10	..	..	40
Meat	1	8	..	2	50
Total	50⅓	81	127	52½	1,300

Fats should be avoided as carefully as carbohydrates. They are exceedingly harmful, except as they occur in protein milk and pot cheese. Cod liver oil is no exception, and is often the cause of trouble. When improvement has taken place, butter may be tried and is often successful. Vegetables may be added early but carefully.

The caloric requirement, as shown by the charts, is from two to three times the normal, approximately one hundred calories per pound being required in the early stages of treatment. This diminishes with improvement, as does the voracious appetite of this stage.

Treatment to be successful should be continued for an indefinite period. Some cases present a tolerance early for bread crust or rusk, some not for a long period. Only experience with the individual child will set the time. Up to the present moment it seems that all these cases sooner or later will react normally to most foods.

Blood transfusion, although it failed in our case, is a very valuable procedure.

3. Ashford, quoted by Siler, J.: Proc. Pan-Am. Sc. Cong., 1915-1916, **10**:12-18, 1917.

It is not to be expected that the institution of the above treatment will be successful at once. On the contrary, in severe cases the first four or six weeks are apt to be most discouraging. The first sign of improvement is change in disposition. The infant becomes happier and smiles, the appetite improves, and only after hunger has been established may a gain in weight be expected. Renewed growth comes much later. An early sign of improvement is yellow stools. Once improvement has set in there are rarely any setbacks and these only slight, usually dependent on some intercurrent infection to which these children seem prone.

The treatment as applied to a specific case presents a composite picture somewhat as follows. In a case of moderate severity there is usually an immediate history of vomiting and diarrhea, more or less edema, the child is peevish and querulous to the last degree, refusing food, crying constantly, not sleeping, with the weight stationary or declining. A half ounce (15 c.c.) of castor oil is administered, protein milk offered. If this is refused, protein milk prepared with one of the several preparations of calcium caseinate, and colonic irrigations of sodium bicarbonate twice daily are given. Under this treatment there is very little visible improvement for the better part of a week. The best that can be hoped for is that the diarrhea is controlled, the child becomes a little more comfortable, and the protein milk taken with some degree of relish, the weight usually declining. Other foods are now offered, orange juice, broth, banana, gelatin and cottage cheese. One or more of these may be accepted, possibly none. The stools, however, improve, become yellow, and the child is definitely less unhappy. This condition may persist anywhere from four to eight weeks until the child accepts banana which should be offered daily, and sooner or later bananas will be taken. Then only does the weight begin to improve, although in every other respect improvement may have already taken place. From this time on there is rarely any interruption in the gain, nor are there relapses unless owing to an intercurrent infection or some gross fault in management, and the relapse is never a complete one, as it is seen so characteristically in this condition, but is represented chiefly by a loss in weight which is rapidly recovered, the entire relapse being relatively not more than may be expected in a normal child passing through an acute infection. An illustrative case may be of value in showing the difficulties which confront one. Case 5, R., a girl, aged 12 months, was first seen Oct. 10, 1922, when she weighed 12 pounds 4 ounces (5 kg.). Castor oil was given at regular intervals, sodium bicarbonate irrigation carried out daily. The diet such as outlined above was attempted, but everything was refused excepting the albumin milk, with the result that it was not until two months after treatment started that any real gain was made, her weight on December 12 being 12 pounds

14 ounces (5.9 kg.). It was at this time that she began to take a single banana in addition to the albumin milk, pot cheese and broths in which vegetables had been cooked, although the stools were normal. From this time forward the result was better, so that by Jan. 15, 1923, the weight had risen to 15 pounds 2 ounces (6.8 kg.), and she was taking four bananas in addition to her previous feeding.

The following histories will illustrate the effects of treatment.

REPORT OF CASES

CASE 1.—A girl, aged 15 months, first seen, June 3, 1919. At birth she weighed 6½ pounds (2.7 kg.). Her weight June 3 was 18 pounds, 10 ounces (8.2 kg.). She was the first and only child of normal birth. At 10½ months she weighed 17 pounds (7.7 kg.). The gain was slow.

Previous diet.—She was never breast fed, but was given first simple milk mixtures. Jan. 20, 1919, skimmed milk, water, dextrimaltose, farina, beef juice. January 30, she had malt soup mixture, farina, beef juice. June 4, fruit, cereal, egg, vegetables, split pea soup. Formula: milk lime water, dextri maltose. June 22, she had malt soup, potato and vegetable soup.

There was a history of periodic gain with attacks of diarrhea and anorexia and rapid loss of weight.

Physical examination showed an extremely pale child, markedly protuberant abdomen, very peevish, with fontanel almost closed. She had four teeth. The spleen and liver were palpable; the patient walked with the body thrown backward from the hips to compensate for the large abdomen. The diet at this time was: whole milk, 25 ounces, imperial granum, 1½ ounces given by bottle, each of 8 ounces, dextrimaltose, 1 ounce, water, 15 ounces.

The schedule was: at 7 a. m., bottle; at 9 a. m., orange; at 11 a. m., egg and bottle; at 3 p. m., broth, 5 ounces of potato and bottle; at 7 p. m., bottle.

Approximately 1,000 calories or 55 per pound.

This diet, with unimportant changes, was continued as the child was being taken to the country from which she did not return for three months, during which time she grew worse. At this time the treatment which has proved successful in all of our cases, was begun. The drop in the weight curve during the second year was due to an attack of measles and pneumonia. The flattening during the third year was due to an insufficient caloric intake. At the present time this child is entirely normal. She takes upward of 20 ounces (591 c.c.) of milk daily, an occasional egg, cereal and bread regularly, and occasionally ice cream. At the age of 6 years her height is 47 inches (119 cm.), her weight 50½ pounds. (22.7 kg.). There is no protuberance of the abdomen, the stools are normal, and she is in all respects a healthy child.

CASE 2.—D. S., a boy, aged 4 years, was presented for treatment Oct. 10, 1921. His weight at that time was 20 pounds, 14 ounces (9 kg.). His height, 33 inches (84 cm.).

He had been brought to the office Oct. 7, 1920, presenting the same symptoms only to a less degree. At that time his weight was 19 pounds (8.6 kg.) and his height 33 inches (84 cm.). During the year there had been practically no gain in weight, the discrepancy being due to the increased edema, and no gain in the height. The family history was negative, the patient was the first of two children, born at full term, and a forceps delivery. There was bleeding from the umbilicus, and generalized subcutaneous hemorrhages, lasting several days. There were no bleeders in the family. The patient had scurvy (?) when 7 months old, for the duration of two weeks. Again at the age of 2 years, while on a general diet, which however contained no vegetables, and again when 2 years and 3 months old. The hands, feet and face swelled up and there was a history of vomiting, anorexia, and thin stools during attacks. When the

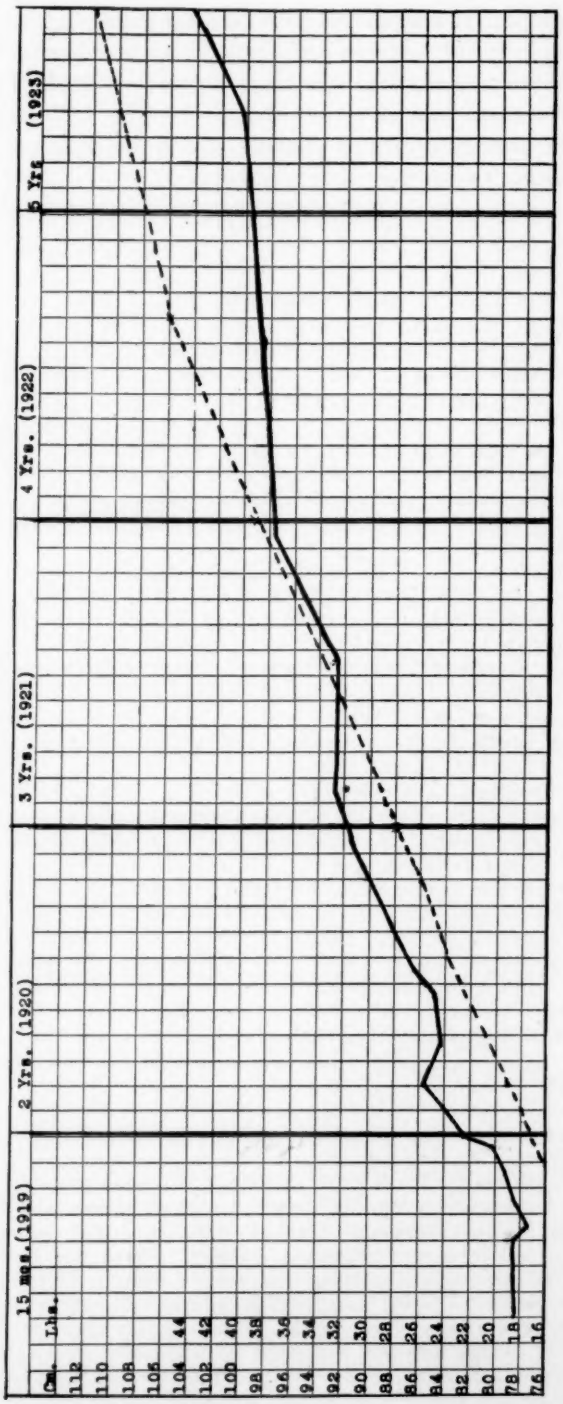

Fig. 1 (Case 1).—Progress of R. L. Broken line indicates height, straight line, weight.

patient was brought the second time, he was receiving the following daily diet: At 6 a.m., 8 ounces of protein milk, at 10 a.m., farina, bread and butter, protein milk, at 2 p.m., strained vegetable soup, rice and carrots, hard boiled egg, cottage cheese, at 6 p.m., cottage cheese, protein milk, bread and butter, and at 10 p.m., protein milk.

The physical examination at this time showed a child, who although 4 years old, seemed to be an infant in arms, being carried in on a pillow. He had never stood or walked. The most striking feature was the intense pallor, and the unhappy facies, the patient whimpering constantly. When stripped, the abdomen showed great distention, (circumference 63 cm.). His legs were flexed, the thighs abducted in a frog posture. They were practically without power. Handling seemed to cause him pain. The mouth was sore and the child seemed to avoid the light. The edema was marked. There was considerable free fluid in the abdominal cavity. The following diet was ordered.

At 6 a. m., 9 ounces (266 c.c.) of albumin milk; at 8 a. m., orange and one banana; at 9 a. m., one banana, 7 ounces (207 c.c.) of albumin milk; at 12 noon,

Fig. 2 (Case 2).—D. S., aged 5½ years, to the left. Compare with a younger brother, aged 4½ years.

scraped meat, two tablespoonfuls. Albumin milk, 7 ounces; 3 p. m., 9 ounces albumin milk; 6 p. m., whites of two eggs. Gelatin, ½ ounce (15 c.c.). Albumin milk, 7 ounces; 10 p. m., albumin milk and banana.

This was soon increased, more bananas being given, and pot cheese added as detailed in the chart. Sodium bicarbonate irrigations were used once or twice daily, and a dose of castor oil given once a week. On this diet the edema, tenderness, anorexia, and diarrhea disappeared. The child became happy, began to have a healthy color, and progressed uninterruptedly as Figure 3 shows, excepting for a short period of underfeeding last summer when his weight fell off slightly, but with no symptoms of disease. At the present time he is a ruddy looking child, playful, walks and runs, and is quite normal in every respect except that he is underweight and undersized for his age; and that carbohydrates with the exception of banana, must be very carefully restricted, and milk as such omitted entirely. When last seen on May 26, 1924, at the age of 6½ years his weight was 45 pounds (20 kg.) and his height 43½ inches (111 cm.)

CASE 3.—J. R., a girl, aged 17 months, came under observation April 14, 1922. Her birth weight was 7 pounds 2 ounces (3.2 kg.). She was the second child, of instrumental delivery. She was not breast fed. She had solid food at the age of 7 months. The child had been for some time at the Baby's Hospital, where she was seen in consultation by a number of physicians. The diagnosis made was tuberculous peritonitis.

There was a history of alternate attacks of diarrhea accompanied by vomiting, and massive stools. The symptoms when first seen were: diarrhea, vomiting, edema, protuberant abdomen, hyperesthesia, photophobia and marked irritability. The child at this time was receiving a liberal diet including cereals. She was then ordered ½ ounce (15 c.c.) of castor oil to be repeated weekly, and colonic irrigations of bicarbonate of soda, to be given twice daily. Protein milk was prescribed, to be sweetened with saccharin. In addition pot cheese, broth, gelatin, banana, orange, and scraped meat were ordered. For a short time, as is usually the case, there was little taken except protein milk. Within a short time the irritability, tenderness, edema and photophobia disappeared. The child smiled and was happy and contented. The stools became yellow, and as time went on she took more of the food allowed, so that after a few months the diet

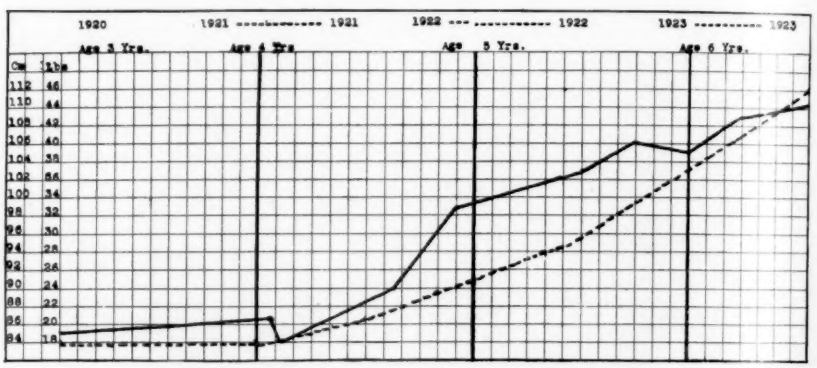

Fig. 3 (Case 2).—Progress of D. S. Broken line indicates height, straight line, weight.

was as follows: 6 a. m., whites of 2 eggs, and 12 ounces (355 c.c.) of albumin milk; 8 a. m., 1 orange; 10 a. m., three tablespoonsful of finely minced meat, with a tablespoonful of spinach, peas or beans, albumin milk, 12 ounces (355 c.c.); 2 p. m., gelatin 8 ounces (236 c.c.), 2 bananas; 6 p. m., 3 bananas, albumin milk 12 ounces; 10 p. m., albumin milk 12 ounces. The total albumin milk was 48 ounces (1,419 c.c.), and 5 bananas daily.

No patient had more marked hydrolability than this child. The daily fluctuation in weight in the early weeks was often 1 pound (0.5 kg.) or more, and long after she was well on the road to recovery, the degree of perspiration was amazing. While watching the skin, drops the size of a split pea could be seen to form, coalesce with others, and run down literally in a stream. Large quantities of water were also passed by the kidneys. This was regular for all the patients. Figure 4 shows a drop in weight at the age of 25 months which was due to an acute infection. The flattening, which occurred at the age of 31 months and lasted to the age of 35 months, resulted from underfeeding while away for the summer. When last seen, Feb. 4, 1924, the weight was 35 pounds 2 ounces (15.9 kg.) and the height 94 cm. She was well and appeared ruddy, happy and healthy. This child was taking small amounts of carbohydrate other than banana.

CASE 4.—R. S., a girl, aged 1 month, was first observed June 27, 1918, at the Home for Hebrew Infants. Her weight was 6 pounds 9 ounces (2.7 kg.). She was given albumin milk for two weeks, then put on a simple milk modification. Physical examination at this time revealed a slightly undernourished baby, but nothing to suggest a future disturbance, unless the loose bowels and scalded buttocks could even at this early date have represented a carbohydrate intolerance. The progress was slow but steady until the age of 9 months, when an attack of grip occurred, and at the age of 13 months an attack of enteritis, with rather considerable loss of weight. At 9 months cereal was added to the diet. Her condition at this time showed symptoms of rickets. She was underweight

TABLE 2.—*Height and Weight of Case 2*

Age, Years	Intake		Weight			Height				
								Normal		Difference
	Total Calories	Per Pound	In Pounds	Normal	Difference	In.	Cm.	In.	Cm.	Cm.
4 1/12	1,300	67	19½	37	17½—	33	83½	40	101½	18—
4 2/12	1,250	62	20½	37½	17—	..	..	..	....	.....
4 8/12	1,300	56	23¾	38	14¼—	..	..	..	....	.....
5 6/12	1,200	49	24½	39	14½—	33	83½	41½	105	21½—
4 7/12	1,500	48	30¾	40	9¼—	33	83½	42	106	22½—
4 10/12	1,500	48	33	42	9—	37	94	42½	107	12—
5	.....	..	..	..	....	..	..	....	....	....
5 1/12	.....	..	34	43	9—	37	94	43	109	15—
5 3/12	1,620	44	39	45	6—	37½	95	44½	113	18—
5 8/12	.....	..	40	46	6—	39	99	45	114	15—
6	1,400	35	39½	48	8½—	41	104	46	117	13—

TABLE 3.—*Height and Weight of Case 3*

Age, Months	Intake		Weight			Height				
								Normal		Difference
	Total Calories	Per Pound	In Pounds	Normal	Difference	In.	Cm.	In.	Cm.	Cm.
17	600	..	15¼	23½	8¼—	29¼	74	31	79	5—
18	1,250	78	15¾	24	8¼—	29¼	74	31½	79¾	5¾—
19	1,375	78	19	24	5—	29¼	74	31½	80	6—
20	.....	..	21¾	24½	2¾—	30	76	32	81	5—
21	.....	..	22	25	3—	..	..	..	..	....
22	1,050	44	23½	25½	2—	30¼	77	32½	82	5—
23	1,100	44	25	26	1—	30½	77½	33	83	5½—
24	1,140	42	26¾	26½	¼+	31¾	80½	33½	85	4½—
25	840	33	26½	27	½—	32	81	33¾	86	5—
26	950	35	27	27½	½—	32	81	34	86½	5½—
27	.....	..	..	..	....	..	..	..	..	.....
28	1,050	36	29	28	1+	32	81	34¾	87	6—
29	1,000	33	30½	28½	2+	32½	82½	35	88½	6—
30	1,000	33	30	29	1+	33	84	35¼	89¾	5¾—
..	.....	..	..	..	....	..	..	..	..	....
..	.....	..	..	..	....	..	..	..	..	....
..	.....	..	..	..	....	..	..	..	..	....
..	.....	..	..	..	....	..	..	..	..	....
35	800	27	29¾	31	1¼—	35¼	89½	36¾	93	3½—
39	.....	..	33¾	32¾	1+	36¾	94	37¾	96	2—

and in a generally unsatisfactory condition. Distended abdomen was noted at this time, but was supposed to be part of the rachitic picture. From then forward, as seen in Chart 4, there were numerous fluctuations in weight, with practically no increase up to the third year when the condition was fully recognized. From the age of 2 years edema was present, on and off. The child was peevish and unhappy and would sit on the floor watching the other children at play. There was definite photophobia as though she were suffering from keratitis, although this was not present. Anemia was marked. The patient was tender to the touch, with occasional skin manifestations such as urticaria and erythema. A severe stomatitis existed most of the time. The urine at intervals showed

albumin and granular hyalin casts. Anorexia was marked. All kinds of diets were tried, and in all combinations. Autogenous vaccines were made from intestinal contents. There was blood transfusion. At intervals the symptoms subsided and the appetite and weight would improve. There was always a relapse, until the end of 1921 when the diet described in this paper was instituted with the result that there was considerable improvement, which however was lost later on the addition of high sugar. At the end of 1922 a rigid diet was instituted, from which carbohydrates were as completely excluded as was possible, with the result shown in Chart 4. This child is doing well, growing and gaining weight. Departure from the diet or regimen is accompanied by some return of symptoms. The drop in weight in the middle of 1923 represented a

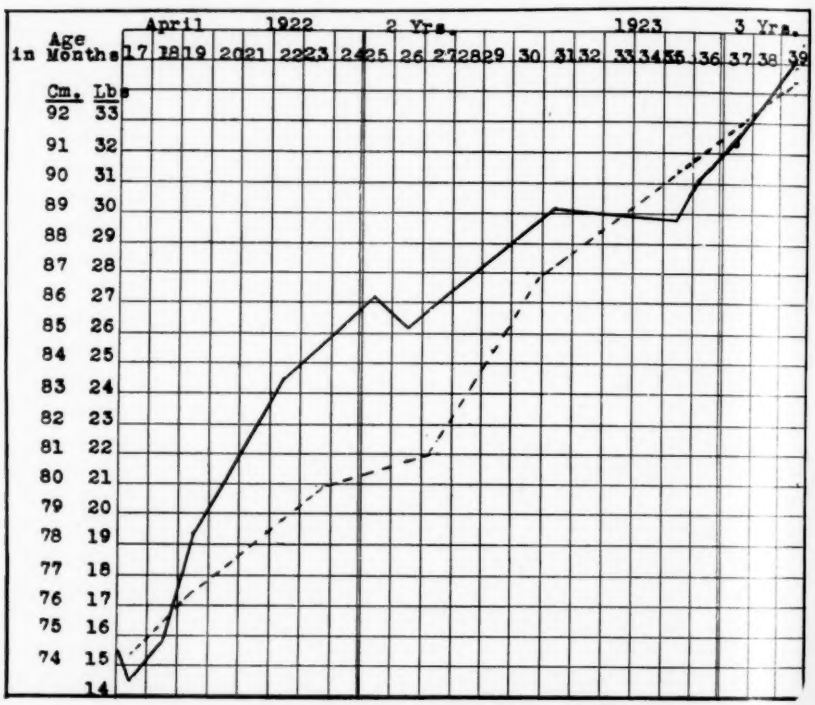

Fig. 4 (Case 3).—Progress of J. R. Broken line indicates height, straight line, weight.

period of bad management owing to my absence from the service, and the disinclination of those in charge to modify the orders. So far as I am aware this is one of the few cases, if not the only case under steady observation from birth, for such a long period.

CASE 5.—R. G., a girl, aged 1 year, came under observation Oct. 10, 1922. Her birth weight was 8 pounds 3 ounces (3.6 kg.). She was the first child, of normal labor. She was never breast fed. Her diet consisted of Dryco for three weeks. Milk, lactose, lime water, barley water. Malt soup. Milk, water and cane sugar. Evaporated milk, granum and Eskay's food.

At the age of 6 months final radium application was made for the removal of an obstructive thymus gland. The patient's highest weight was at 8 months when she weighed 13 pounds 5 ounces (5.9 kg.). She had been gaining 1 pound

Fig. 5 (Case 4).—Dec. 15, 1922. Patient in the center. Contrast with normal children of the same age.

Fig. 6 (Case 4).—May 30, 1923. The same group as Figure 5. Note the progress of the patient, R. S., in the center.

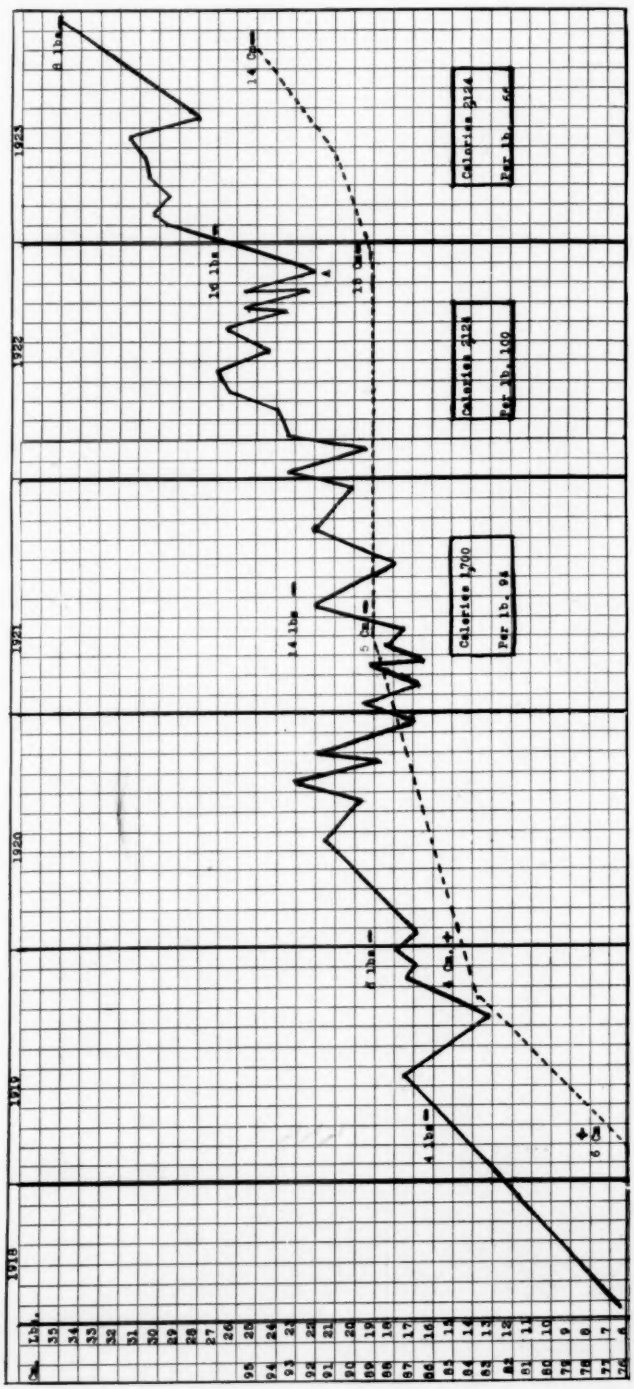

Fig. 7 (Case 4).—Progress of R. S. Weight, straight line, length, broken line.

(0.5 kg.) a month up to the fifth month. Her diet when first seen was, barley, 5 tablespoonfuls; Dryco, 20 tablespoonfuls; glucose, 1 ounce (30 c.c.); water, 40 ounces (1,183 c.c.), divided into 5 bottles; orange, farina, beef and broth, 750 calories, or 62 per pound.

Physical examination: Slight edema was seen. One hand and sometimes other parts showed an erysipeloid-like urticaria. The child had a markedly distended abdomen. This case, as well as Case 4 showed a most marked photophobia. There was considerable tenderness on handling. There was loss of power in the extremities. The patient seemed dangerously ill. Fuller details of this case were given in the foregoing. When last seen Feb. 26, 1924, at the age of 28½ months, her length was 86 cm., and her weight 26 pounds 12 ounces (11.8 kg.). A recent attempt to feed one tablespoon of oatmeal daily produced anorexia and diarrhea.

Case 6.—R. S., a boy, aged 13 months, came under observation Nov. 6, 1922. He was the first child of cesarean birth, with a weight of 9 pounds (4.1 kg.). He was breast fed for three weeks. He then received alternately, evaporated milk and granum; milk, barley water, dextri maltose; malt soup; Dryco. The gain was slow until the age of 8 months. Malt soup mixture. Malt soup mixture plus Dryco. His highest weight was 14 pounds 9 ounces (6.4 kg.) at 8 months.

Table 4.—*Height and Weight of Case 5*

Age, Months	Intake		Weight			Height				
								Normal		Difference
	Total Calories	Per Pound	In Pounds	Normal	Difference	In.	Cm.	In.	Cm.	Cm.
12	.....	..	11½	20½	9—	26½	67	29	74	7—
13	850	71	12	21	9—	....	..	..	..	...
14	1,080	83	13¼	21⅞	8½—	....	..	..	..	...
15	1,095	74	15	22¼	7¼—	26¾	68	30	76	8—
16	1,200	75	17¾	22¾	5—	28	71	31	78½	7½—
17	1,275	67	....	....	....	..	..	..	..	.....
18	.....	..	18¾	24	5¼—	28	71	31½	80	9—
19	1,150	57	20½	24½	4—	29	73½	32	81	7½—
20	1,200	52	22¾	24¾	2—	29¼	73½	32	81½	8—
21	.....	..	23½	25¼	1¾—	30¼	76	32½	82½	6½—
22	.....	..	....	....	.....	....	..	....	....	...
23	1,200	48	24¾	26	1¼—	31	79	33	84	5—
24	1,200	50	25½	26½	1—	32	81	33½	85	4—

He then had diarrhea, anorexia and reduced in weight to 12 pounds (5.4 kg.). When first seen he was receiving Larosan milk for three weeks, cereal, toast, broth, one tablespoon of dextri maltose in each of five 8 ounce (236 c.c.) bottles.

Physical examination: The child showed marked irritability. There was slight edema and tenderness on handling. The abdomen was distended.

When the diarrhea was controlled the stools became massive. On the treatment outlined, recovery was prompt. The stools became yellow. The baby began to look happy. Jan. 9, 1924, he was 84 cm. tall, and weighed 26 pounds 10 ounces (11.8 kg.) and was receiving Larosan milk with 1 ounce (30 c.c.) of cream removed from the top of the bottle, 6 bananas, a good portion of vegetable, meat, whites of two eggs, one slice of bread, broth, and three teaspoonfuls of butter.

Case 7.—M. R., a boy, aged 23 months, was presented for treatment April 27, 1923. His birth weight was 7 pounds (3.2 kg.) He was the second child. The first infant was normal. This patient was breast fed for two months, then breast and bottle fed, and after that had innumerable changes in diet. There was history of frequent attacks of diarrhea, occasional vomiting, excessive irritability and peevishness. He had otitis at about the age of 1 year, croup at the age of 18 months, and was said to have had an attack of intestinal grip at the age of 1 year. He had never walked. Roentgen-ray examination of the legs

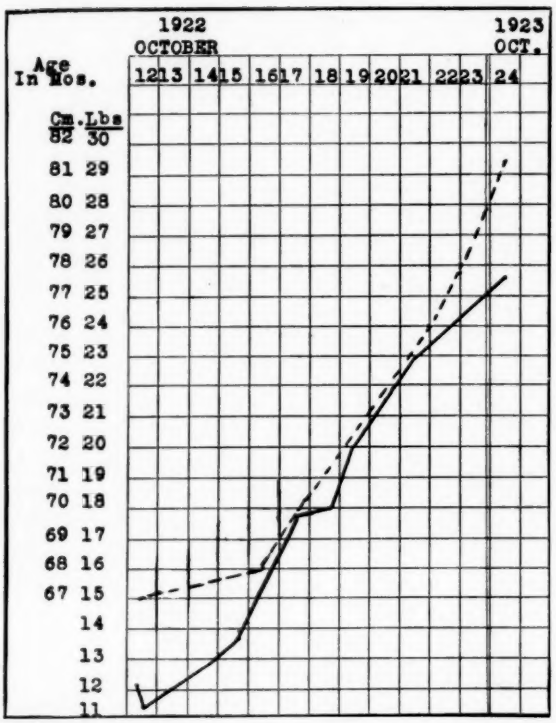

Fig. 8 (Case 5).—Progress of R. G. Broken line indicates length, straight line, weight.

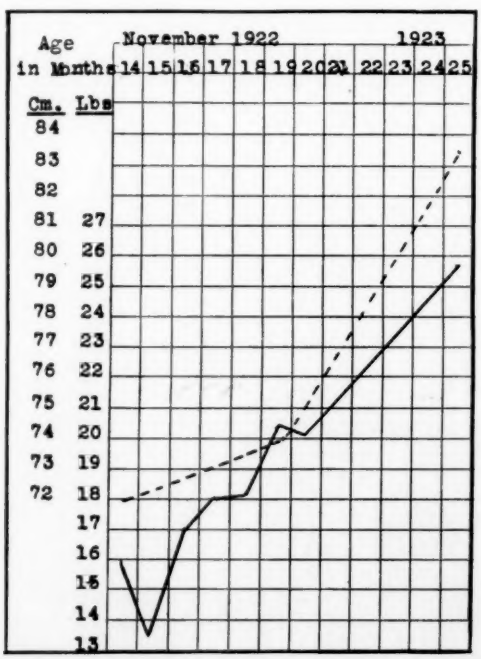

Fig. 9 (Case 6).—Progress of R. S. Length indicated by broken line, weight by straight line.

is said to have shown scurvy and rickets. When he came under observation he was receiving the following diet: 6 a. m., milk, 5 ounces (148 c..c); 8 a. m., orange juice; 10 a. m., farina and milk; 12 noon, soup, meat, vegetables and stewed fruit; 6 p. m., cereal, junket or custard and milk. The total amount of milk daily was 24 ounces (710 c.c.). Total calories 900, or about 53 per pound.

Examination showed a desperately sick baby who looked as though he could not possibly survive. Very marked edema from the hips down was present. This was somewhat less marked in the upper extremities. The abdomen was markedly distended, 48½ cm. in circumference, and contained free fluid. The pallor was extreme. The child whimpered, was peevish and cried when touched. He did not move the lower extremities, and had a tendency to keep the hands over the eyes. The urine contained albumin with several hundred granular and granulohyalin casts to the field. The blood showed a distinct secondary anemia,

TABLE 5.—*Height and Weight of Case 6*

Age, Months	Intake		Weight			Height				
								Normal		Difference
	Total Calories	Per Pound	In Pounds	Normal	Difference	In.	Cm.	In.	Cm.	Cm.
14	900	56	16	22	6—	28½	72	30½	77	5—
15	1,025	70	13½	23	9½—	....	..	..	..	...
16	1,155	68	17	23½	6½—	28½	72	31	79	7—
17	1,000	55	18	24	6—	....	..	..	..	...
18	1,000	50	18	24½	6½—	29	74	32	81	7—
19	1,000	50	20½	25	4½—	....	..	..	..	...
20	.....	..	20	25½	5½—	....	..	..	..	...
21	1,000	45	21½	26	4½—	30½	77	33	84	7—
22	1,000	44	22½	26½	4—	....	..	..	..	...
23	1,100	46	24½	27	2½—	....	..	..	..	...
24	.....	..	25	27½	2½—	32	81	34	86	5—
25	1,300	50	25½	28	2½—	33	83½	34	87	2½—

TABLE 6.—*Height and Weight of Case 7*

Age, Months	Intake		Weight			Height				
								Normal		Difference
	Total Calories	Per Pound	In Pounds	Normal	Difference	In.	Cm.	In.	Cm.	Cm.
23	900	53	20½	27	6½—	29	74	34	86	12—
24	1,100	64	17	27	10—	..	..	..	..	....
25	1,580	72	22	28	6—	29	75	34	87	12—
26	1,760	80	24	28	4—	30	76	34¾	88	12—
27	1,680	62	27	29	2—	30½	77	35	89	12—
28	1,525	55	29	29	Normal	31	79	35½	90	11—
29	1,625	54	30	30	Normal	32	81	36	91	10—

3,400,000 erythrocytes. The hemoglobin was 40 per cent. There was no abnormal cytology. Within four weeks the urine became normal. May 11, the patient was less irritable, smiled for the first time in weeks, the stools were improved, and the edema was much less. May 26, four weeks after coming under observation, there were from four to five stools daily, large, yellow and occasionally green. The child's appetite was ravenous. He was happy and smiled constantly. He received eight bananas, pot cheese made from one quart of milk, 24 ounces (710 c.c.) of milk converted into protein milk by means of calcium caseinate, broth, the juice of an orange, and the white of one egg. June 27, 1923, he was taking from 14 to 16 bananas daily. August 6, 1923, the stools were normal except for an occasional slight amount of mucus. The child was no longer ravenous, and he was able to stand. The perspiration was profuse, with the odor of lactic acid. He was so fat that he looked edematous; he gained almost 3 pounds in eighteen days. October 13, the hemoglobin was 60 per cent.

and the erythrocytes 5,000,000. This child made very rapid progress, and when last seen, Jan. 12, 1924, his height was 85 cm., his weight 32 pounds 14 ounces (14.5 kg.). The stools were yellow and normal. He walked and was happy and well. His diet is still restricted.

SUMMARY

Celiac disease is a nutritional disturbance of late infancy and early childhood, due to inability to utilize fats and carbohydrates in a normal manner. The treatment has presented discouraging difficulties. Carbohydrate in the form of ripe bananas appears to be tolerated perfectly, making it possible to bring about a clinical cure in practically all cases.

Fig. 10 (Case 7).—M. R., aged 2 years. Recovery begun.

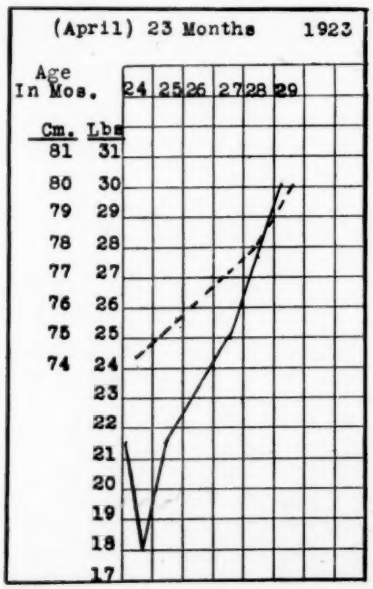

Fig. 11 (Case 7).—Progress of M. R. Length indicated by broken line, weight by straight line.

Whether there is a factor in the banana other than the carbohydrate content which results in this cure is unknown. The treatment of this disease requires a high caloric diet from two to three times the normal. Milk is replaced by one of the lactic acid forms. No other fat is used, and no carbohydrate except ripe bananas, and that present in the lactic acid milk. Proteins may be used in all forms and apparently in any quantity. The maximum number of bananas used in any one case was 16 daily by a child, aged 26 months. In addition to the dietary treatment, a full dose of castor oil is given once a week, and colonic irrigations of sodium bicarbonate daily. Of ten patients, eight so treated have made a clinical recovery. Two patients not so treated died.

MONGOLIAN IDIOCY WITH TEETH OF HUTCHINSON'S TYPE

REPORT OF CASE *

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ROCHESTER, MINN.

One hundred fifty-five cases of mongolian idiocy have been observed at the Mayo Clinic in the last few years, but the case reported here is the only one of the series in which there were typical and unmistakable Hutchinson's teeth. The typical Hutchinson's incisor generally has been

Typical Hutchinson's teeth in a case of mongolian idiocy.

considered as pathognomonic of congenital syphilis. However, in this child no other stigmas of syphilis were present, and the blood Wassermann reaction was negative.

REPORT OF CASE

History.—A girl, aged 8 years, was brought to the Clinic March 23, 1924, because of mental backwardness. Her mother, aged 37, and her father, aged 42, were both healthy and normal mentally. The child was the youngest of three children, the other two being alive and well. She was a full-term infant and delivery

* Received for publication, July 8, 1924.

was spontaneous. Her weight at birth was estimated to be 6.75 pounds (3 kg.). She was breast fed entirely for four months, after which she received a mixed diet. She developed slowly. The first tooth erupted when she was 13 months old, and she did not begin to walk until she was 2.5 years. Speech was delayed until she was 3 years, and even at the age of 8, she did not talk intelligently. She was unable to control the bowel movements until the age of 5 years. At present she is difficult to manage and does not seem to understand what is said to her.

Examination.—It was seen at once that the child was a typical mongolian idiot. She was alert and restless and not in the least apathetic. Her mentality was that of a child of about 2.5 years. She was 43 inches (109 cm.) in height, 12 inches (30.48 cm.) below the average height for her age. She weighed 45 pounds (20.4 kg.), 4 pounds (1.8 kg.) more than the average for her height. Her hair was only slightly coarser than normal. Her head was short and round, of the brachycephalic type, making the bridge of the nose appear lacking. The occiput was somewhat flattened. Internal epicanthic folds were marked. Blepharitis was present. Nystagmus was present, due to a right central corneal opacity, which the ophthalmologist said was the result of an old ulcer and probably not due to syphilis. Her tongue was large and coarse in appearance with prominence of the circumvallate papillae. The skin, especially that of the face, was rough, dry and slightly scaly. Her fingers were short and thick, and did not taper; the little fingers curved inward. The joints were unusually lax. An umbilical hernia was present.

Twelve permanent teeth were in position; all were more or less deformed. The permanent upper central incisors were typical Hutchinson's, with the central concavity on the biting edges, and the lateral borders definitely rounded (see illustration). All lateral incisors and the two lower central incisors had poorly developed crowns, but otherwise were normal. The sixth-year molars also had irregular and poorly developed crowns. All of the temporary teeth were badly decayed. The Wassermann blood test was negative.

CONCLUSIONS

From this case it appears that in rare instances Hutchinson's teeth may not be pathognomonic of congenital syphilis. In the 155 cases of mongolian idiocy, the Wassermann test on the blood was performed routinely, but in not a single case was it found to be positive.

A CASE OF HEREDITARY CONGENITAL ABSENCE OF THE SALIVARY GLANDS*

WALTER R. RAMSEY, M.D.

ST. PAUL

M. L., a girl, was first seen two years ago, aged 3 years. She was of normal birth and was breast fed for one year. There were three other children, all of whom were normal. The past history of the patient was unimportant, there were no previous illnesses.

The child was brought in because the teeth were badly decayed and the mouth constantly dry.

The mother said that when nursing, the milk would collect around the inside of the lips and cheeks and become dry. She would always have to wash it off with wet cotton before the next nursing. The tongue and mouth always seemed dry.

The condition of the mouth on examination was then as follows: The teeth were discolored, the gums retracted around the teeth, so that they seemed to be stuck in the jaws at irregular angles.

The child ate well, but had to take drinks of water with almost every mouthful in order to be able to swallow the food.

To see if there was any secretion from possible rudimentary salivary glands, sweets as well as acids were given, but there was no evidence of any secretion.

The mother says the father of the child has a similar condition.

I lost contact with the family for two years, and did not see them again until recently, when the mother brought another child in for examination.

I have recently examined the girl, now aged 5 years, and there is no change, except that all of the deciduous teeth are gone and several well formed permanent teeth have appeared.

I went to the house and examined the father's mouth carefully. The condition is identically the same as that of the child. He says that since he can remember he never could expectorate like other boys, and never knew what it was to swallow saliva. All of his teeth were decayed years ago, and he wears false teeth both above and below.

Four other children, all girls, are fairly normal, and wholly so regarding the salivary glands.

The case is interesting from two points of view:

1. A rare condition.
2. An illustration of heredity.

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* Received for publication, June 27, 1924.

* Read before the Thirty-Sixth Annual Meeting of the American Pediatric Society, Pittsfield, Mass., June 5-7, 1924.

EXAMINATION OF PLASMA PROTEINS IN INFANTS*

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Our knowledge of the proteins of the blood plasma of infants has been very limited, due to the difficulties in methods of study. The small amount of blood available was not sufficient for an exact chemical analysis. The few examinations reported in the literature were limited to the determination of the so-called "colloid lability." It is only since one of us [1] published a simple nephelometric method that it has become possible to study the protein fractions in 1 c.c. of blood, and to undertake examinations in a large number of cases. We examined more than one hundred healthy and sick infants. This test is based on the following principle. It has been known since Hofmeister's time that a half saturated ammonium sulphate solution precipitates all the globulins and fibrinogen; a 33 per cent. saturated solution precipitates the euglobulin and fibrinogen; and a 27 per cent. saturated solution will only precipitate the fibrinogen. It was noticed that by using small amounts of protein material the above solutions give no precipitates but only an opacity, which is very well adapted for a nephelometric test. The standard cloudiness is always the whole precipitate gained from the plasma of the material, to be examined after it has been treated with acid ammonium sulphate solution. It is a very simple matter to calculate the relative quantitative relation of the albumin, pseudoglobulin and euglobulin and fibrinogen from the nephelometric readings of the whole protein. If the protein content of the plasma under examination is known (refraction, Kjeldahl, etc.) the absolute content of the before mentioned protein fractions can be determined therefrom.

The determination of all the protein fractions including the calculation takes no more than fifteen minutes and only requires 1 c.c. of citrated plasma. These are the reasons that make this method primarily adaptable for clinical use.

Blood was obtained from the longitudinal sinus of fasting infants. Quantitative nephelometric tests were performed for the protein frac-

* Received for publication, July 3, 1924.

* From the Clinics of the Royal Hungarian Elizabeth University, at present in Budapest, Prof. P. Heim, Director; and from the third Medical Clinic of the Royal Hungarian Pasmany Peter University at Budapest, Baron A. von Koranyi, Director.

1. Rusznyak, S.: Biochem. Ztschr. **141**:479, 1923.

tions, and also the following lability tests, Frisch-Starlinger,[2] Gerloczy,[3] Daranyi.[4] The first two are carried out with the plasma, and usually run parallel with the fibrinogen content; the third is carried out with serum and usually, but not always, coincides with the globulin contents. Finally we tested the rapidity of the descent of the erythrocytes in the Linzenmeier[5] tube, this last test according to our experience depends on various factors.

On the basis of data found in the literature[6] we first examined conditions in healthy infants, and found that the conditions characteristic of the new-born remain unchanged until the middle of the second month when they take on the characteristics of older infants. The blood of a new-born babe is very low in fibrinogen, rich in globulin and total albumin; erythrocytes drop very slowly. The Frisch-Starlinger and Gerloczy reactions are negative, while the Daranyi is positive. All this changes up to the second month (Charts 1 and 2). The fibrinogen content gradually increases while the globulin diminishes slightly. The albumin content, after a primary decrease, finally reaches quite a high level which is so distinctive of infancy. At the same time the red blood cells drop rapidly and the Daranyi's reaction becomes negative.

These phenomena justify the conception of a "biologically functioning new-born period" which extends into the second month of life, and its well known clinical characteristics can be brought into harmony with the results of our blood examinations. There may also be some connection between the low albumin content of the blood at this period and the large quantity of fluid in the tissues, and the great hydrolability and susceptibility to enteral septicemia and other infections. The

2. Frisch-Starlinger reaction, Med. Klin. **2**:72, 1923: 0.2 c.c. citrated plasma plus 0.2 c.c. of a concentrated solution of sodium chlorid. Read the precipitate after three minutes at room temperature.

3. Gerloczy's reaction, Klin. Wchnschr. 1922, 43: 0.3 c.c. of plasma is put into several test tubes. Add the same amount of various salt solutions which are isotonic with physiologic salt solution. The following salt solutions are necessary: potassium sulphate, 2.54 per cent.; potassium chlorid, 1.8 per cent.; potassium bromid, 1.73 per cent.; potassium nitrite, 1.47 per cent.; potassium iodid, 2.42 per cent.; potassium sulphocyanate, 1.41 per cent. Water bath at 50 C. Slow increase of temperature (the best method is to increase it 1 C. every three minutes) up to 60 C. The strength of the reaction is judged from the number of test tubes in which the precipitation has set in.

4. Daranyi's reaction. Deutsche Med. Wchnschr. **48**:553 (April) 1922. 0.2 c.c. serum plus 1.1 c.c. of diluted alcohol (the latter is prepared as follows: 1.0 c.c. of alcohol, plus 4.1 c.c. of 2 per cent. sodium chlorid solution, which is made from a 10 per cent. standard solution). Water bath for twenty minutes at exactly 60 C., reading of the flake formation after one-half, one, two, three and twenty-four hours.

5. Linzenmeier's test. Zentralbl. f. Gebr. u. Gynak. **46**:1873 (Nov.) 1922: Add citrated blood to the upper mark of the Linzenmeier tube and note the time when the blood column descends to the lower mark. Room temperature.

6. Duzar: Jahrb. f. Kinderh. **100**:237 (Dec.) 1922.

inability to form antibodies in the first two months seems to be due to the obvious absence of fibrinogen. The presence of the antibodies obtained from the mother is probably due to the great globulin content, since recent investigations have shown that antibodies are connected with the globulin fraction.[7] Likewise the nonspecific Wassermann reac-

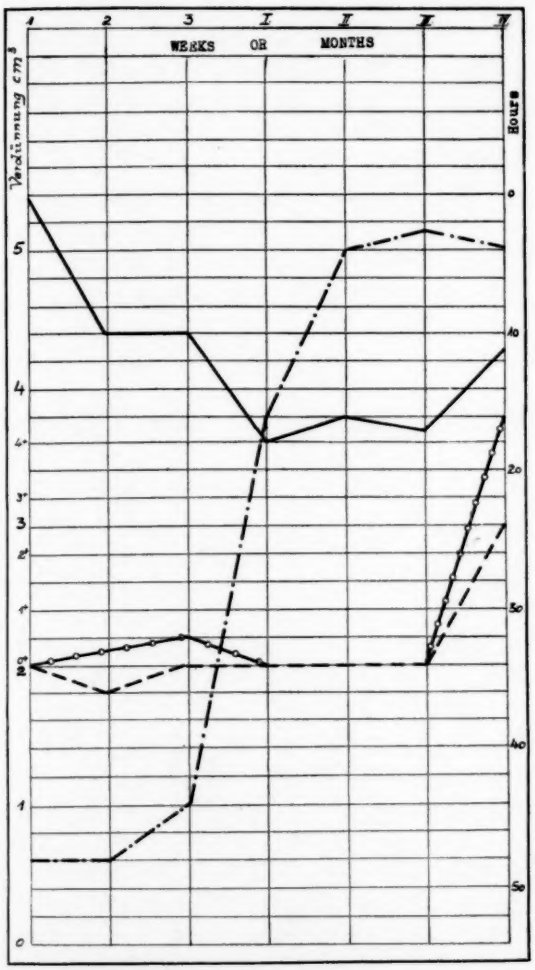

Chart 1.—Straight line, Daranyi's reaction; dash and hollow dot line, Gerloczy's reaction; broken line, Frisch-Starlinger's reaction; dot and dash line, red cell sedimentation.

tion in the new-born may be due to the great amount of globulin, while the reduced globulin content (serum stability) in the second month may

7. Berger: Klin. Wchnschr. **2**:1176-1180 (June 18) 1923; **2**:1226 (June 25) 1923.

account for the negative Wassermann reaction in a syphilitic infant. It is interesting to note that according to Ylppö [8] the relative acidosis of the intermediary metabolism of the new-born, as well as the hyperbilirubinemia and the poor osmotic regulative power,[9] all signs of liver hypofunction, do not disappear until the second month.

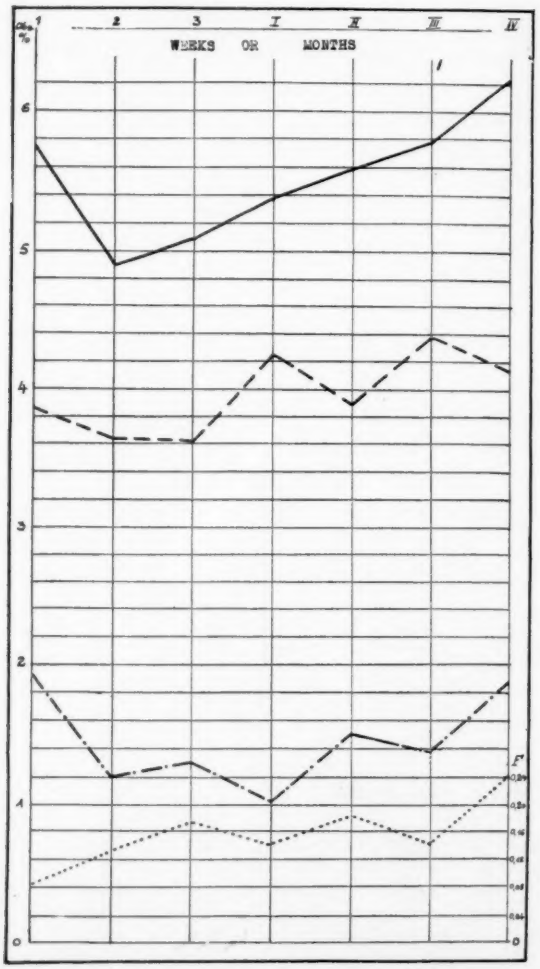

Chart 2.—Total protein, straight line; albumin, broken line; globulin, dot and dash line; fibrinogen, dotted line.

In our investigation of pathologic cases the first aim was only orientation. We shall discuss briefly only those cases which showed

8. Ylppö: Ztschr. f. Kinderh. **14**:268, 1916.
9. Salge: Ztschr. f. Kinderh. **11**:88, 1914.

a very marked deviation from the normal. A marked fibrinogen increase is to be noted especially in icterus neonatorum, in intoxications and in congenital syphilis. In all such cases the Frisch-Starlinger and Gerloczy reactions were markedly positive.

In icterus, however, the sedimentation of the erythrocytes in the blood of young infants was very much protracted (twenty-four hours), while in intoxications and congenital syphilis the rate was markedly increased (sometimes only from nine to ten minutes). In icterus this is supposed to be due to a diminished functioning of the liver, while in intoxications and syphilis, on the other hand, to an injury to the liver. These theories are difficult to reconcile with the increase in fibrinogen, since in the liver of adults hypofunction usually causes a decrease in fibrinogen. To explain this paradoxical phenomenon, one must consider on the one hand that the function of the liver in the infant, as in the hemoclastic phenomenon, is different from that of the adult, or that on the other hand, an infectious component may account for the increase of fibrinogen in these diseases.

In icterus and syphilis we also found a measurable globulin increase and positive Daranyi's reaction, while in uncomplicated intoxications we found no globulin increase, but the albuminglobulin quotient still remained high.

In acute bronchopneumonia and tuberculosis we found a marked increase in globulin. This increase in pneumonia was not always associated with an increase in fibrinogen, and it disappeared on recovery. The Frisch-Starlinger and Gerloczy reactions were negative, and the Daranyi positive, and the rate of the descent of the erythrocytes slightly decreased. In tuberculosis it is different; the globulin increases parallel with the severity of the process, and an increase in fibrinogen is associated with the progress of the disease, the Frisch-Starlinger and Gerloczy, as well as the Daranyi reactions are positive, and the descent of the erythrocytes is markedly diminished. It is noteworthy that in very severe cases the Daranyi reaction is very weak in spite of the large globulin content.

In chronic pneumonia, after the disappearance of the acute symptoms, the globulin decreases to normal and, curiously, the fibrinogen increases: the Daranyi becomes negative and the Frisch-Starlinger and Gerloczy positive.

This behavior is so characteristic that we often made our differential diagnosis between pneumonia and tuberculosis on the ground of the changes in the plasma proteins.

The determination of the condition in atrophic ("decomponierten") infants is most difficult, since pure decomposition without complications is very rare. In uncomplicated cases one usually finds a decrease in the total albumin content (hydremia with a slight increase in globulin),

a negative Daranyi, the Frisch-Starlinger and Gerloczy weakly positive at times, and an accelerated falling of the erythrocytes, due perhaps to the diminished viscosity.

It was interesting to find increased globulin in Leiner's dermatitis, in marked contrast to the decreased globulin content in the exudative diatheses.

CONCLUSIONS

Our investigations have already brought about several important results. We determined the condition in normal infants and also showed the influence of age and of pathologic processes on the plasma proteins. The characteristic changes in certain diseases give us hope that the protein fractions not only will prove to be important from a diagnostic point of view, but will also permit a deeper insight into the pathologic changes which take place in the body.

OBSERVATIONS ON THE METABOLISM OF RECURRENT VOMITING*

S. G. ROSS AND HUGH W. JOSEPHS

BALTIMORE

This paper records some observations made on a patient who suffered from repeated attacks of recurrent vomiting. In recent years much has been written concerning this disease, but we are still ignorant of its exact etiology. The whole subject has been reviewed recently by Marfan.[1] It is worth while to call attention to the fact that among all the investigators, two, Hilliger [2] and Knoepfelmacher,[3] have attacked the problem from a particular point of view, namely, the relationship of the ketosis to the metabolism of fat and carbohydrates.

It was first demonstrated by Marfan, and has been abundantly confirmed by others, that attacks of this disease are regularly accompanied by an early and excessive excretion of acetone bodies in the urine. The early appearance of the bodies seems to show that they are not the result of ordinary inanition from vomiting or anorexia. Our intention was to study the appearance of the ketone bodies in relation to the blood sugar, and to see how rapidly and readily the ketosis might be produced by artificial means, also how amenable it was to measures directed against it.

The investigation was divided into two parts: first, a ketosis was induced by fasting for a short period; secondly, a ketosis was produced by a diet in which the ratio of fat to carbohydrate was high. So far as possible, comparable studies were carried out on children with apparently normal metabolism as controls.

METHODS USED

For blood sugar, the Fitz modification of the Bang method was used because of the convenience in making a large number of determinations on a single person. Blood for determinations was obtained by pricking the finger. A 0.1 per cent. glucose solution was used to standardize these results. This was made fresh each day and the sugar determined on a few drops, using a technic identical with that for blood

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1. Marfan: Les vomissements périodiques avec acétonémie, Arch. de Méd. d. Enf. **24**: (Jan.) 1921.
2. Hilliger: Jahrb. f. Kinderh. **80**:1, 1914.
3. Knoepfelmacher, W.: Monatschr. f. Kinderh. **21**:241 (June) 1921.

determinations. The blood was always taken from four to five hours following the last meal, and at the same time of day, unless otherwise stated.

For the combined carbon dioxid of the serum, the Van Slyke method was used. For the ketone bodies in the blood serum the method of Van Slyke and Fitz was used. The ketone bodies were estimated as grams of beta-hydroxybutyric acid per liter. The ketone bodies in the urine were estimated by the Van Slyke method and calculated as grams of beta-hydroxybutyric acid. Total nitrogen in urine was estimated by the Kjeldahl method, and creatinin by Folin's method.

REPORT OF CASE

CASE 1.—L. S., a boy, colored, was born in August, 1918.

Family History.—Unimportant. The patient was born at term and weighed 5 pounds (2.3 kg.). Examination when he was 9 days old showed him to be normal except that he was small. He was weaned at 8 months of age, and fed on a mixture of two-thirds milk and one-third barley water with sugar added, receiving cereal at times.

When he was aged 11 months he weighed 15¼ pounds (6.8 kg.). At this time he was suffering from an attack of vomiting and diarrheea which accompanied otitis media. He was acutely ill with very severe vomiting, drowsiness and some hyperpnea. He was given a physiologic sodium chlorid solution intraperitoneally and attempts were made to give him small amounts of protein milk, but he continued to vomit; the next day 5 per cent. glucose solution was given intraperitoneally. Following this, the vomiting promptly ceased and he made a rapid recovery.[4]

At the age of 2 years he was admitted to the hospital. He had been well since his previous visit, but on the morning of admission he suddenly became sick with diarrhea, followed shortly by convulsions, unconsciousness and rigidity with opisthotonos. He was comatose on admission, with a temperature of 104 F. Leukocytes, 18,400. The urine contained acetone. Examination of the spinal fluid showed no increase in cells with a negative test for globulin (Pandy). Because of the vomiting and diarrhea, salt solution was given intraperitoneally, and the next day glucose. Following this, recovery was rapid.

The child remained well until March, 1921, when he was 2½ years of age. Then for a few days he had a slight cold in the head accompanied by diarrhea. On March 21, he seemed feverish, suddenly had a convulsion and began to vomit. He was admitted the next day in a comatose condition with a temperature of 98 F. The leukocytes were 16,200 and the child vomited frequently. He regained consciousness following an intraperitoneal injection of salt solution but relapsed again into coma. March 23 he was given glucose solution by rectum. This was followed by rapid recovery.

A month later the boy began vomiting at about 7 a. m., having eaten well the night before. The vomiting was followed by a general convulsion and then the child became stuporous and would rouse himself only to vomit. He was brought to the hospital in this condition at 10 a. m. At this time the urine contained acetone, and his breath smelled strongly of acetone. Leukocytes 28,000. Temperature 98 F. Both ear drums were injected. Blood was obtained at 12 noon for study. The combined carbon dioxid of serum was 34.7 per cent.

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4. It should be noted that the glucose used in this and in the next attack was not given with the idea of any specific curative action, but merely because 5 per cent. glucose and physiologic sodium chlorid solution were used at that time interchangeably for the giving of fluids intraperitoneally.

by volume, the blood sugar 0.037 per cent. The child continued to vomit everything, including water. At 5 p. m. the blood sugar was 0.045 per cent. and epinephrin (1:1,000) 1 c.c. was given; the blood sugar half an hour later was 0.055 per cent. As there was no improvement in the condition of the child, glucose was given by rectum and six hours later the vomiting had ceased. The following day the blood sugar was 0.097 per cent. and the combined carbon dioxid of the serum 57 per cent. by volume.

In order that the effect of a high fat diet might be studied, the patient was put on a diet consisting of 16 per cent. cream on April 20. Eight hours later he began to vomit and continued to do so throughout the night. He was slightly drowsy. On discontinuing the fat diet the next day the child stopped vomiting and became normal again. April 25, a fasting period was begun. The child began to vomit and became drowsy after thirty-two hours. Four hours later he was given glucose by rectum with immediate recovery. In the light of later experience there can be no doubt that this was a typical attack produced by starvation.

Another attack occurred a year later. The child went without supper, after a very scanty lunch. The next morning he had, therefore, fasted for nearly twenty-four hours. He began to vomit, and had a convulsion. He was given 5 per cent. glucose by mouth which he retained, and in a few hours was completely well.

TABLE 1.—*(Case 1) Fasting Period Beginning April 7, 1922, at 8 A. M.*

Date, 1922	Day	Weight, Kg.	Blood Sugar, per Cent.	Carbon Dioxid Combining Power of Serum, per Cent. by Volume	Acetone Bodies in Urine	Creatinin in Urine, Gm.	Total Nitrogen in Urine, Gm.
April 6–7	...	....	0.103	....	....	...	....
April 7–8	1	12.4	0.103 (12 m.) 0.088 (9 p.m.)	62.4	0.07	125	2.24
April 8–9	2	11.5	0.055 (12 m.)	45.3	0.67	139	3.72
April 9–10	3	11.4	0.064 (5 p.m.)	36.5	0.99	138	2.94
April 10–11	4	10.7	0.057	43.9	1.43	114	3.24
April 11–12	5	10.7	0.074	39.3	*1.13 (1.58)	93	*2.58 (3.61)
April 12–13	6	10.7	0.077	43.3	0.79	133	3.64

* This specimen was incomplete, and the values given on parentheses are the values corrected on the basis of normal creatinin excretion obtained during the other days of the experiment.

FASTING EXPERIMENTS

Experiment 1.—May 3, 1921, the child was given breakfast at 8 a. m., and thereafter nothing but water. At 2 p. m. the blood sugar was 0.100 per cent. At 8 p. m. the blood sugar was 0.086 per cent.

May 4, at 10 a. m. the blood sugar was 0.049 per cent. and the child was rather drowsy. At 1 p. m. the blood sugar was 0.054 per cent. The combined carbon dioxid of serum was 41.4 per cent. by volume. Ketone bodies in the blood serum 0.69 gm. per liter.

May 5, after a forty-eight hour fast, the patient was more drowsy but no vomiting had occurred. The blood sugar was 0.042 per cent. The combined carbon dioxid of serum was 36.6 per cent. by volume. Ketone bodies in blood serum 1.24 gm. per liter. At 6 p. m. glucose was given by mouth. Three hours later the blood sugar was 0.131 per cent., and the patient recovered rapidly.

Experiment 2.—April 7, 1922. Since the last admission in 1921 the child had remained perfectly well. The mother had been told never to allow the child to go more than twelve hours without food. The experiment here recorded was begun at 6 a. m., at which time the child had his regular breakfast. The chemical results are given in Table 1, and confirm strikingly the results obtained a year before. During both periods the child was drowsy, but in neither case

was a typical attack produced. There was a difference in the reaction, for in the first experiment there was no tendency to spontaneous improvement, and it was felt wise to give glucose while in the second experiment glucose was not necessary.

The chemical examinations in both instances were similar. There was a rapid drop in blood sugar beginning within from six to twelve hours, which reached its lowest point in forty-eight hours, a result in accord with those of Hilliger and of Knoepfelmacher. There was a coincident fall in the combined carbon dioxid of the serum. The first experiment was terminated at this point, but the second was continued for a longer period. The patient's drowsiness disappeared, and a marked tendency was shown toward a return of the blood and urine findings to normal figures.

CONTROL CASES FOR THE STARVATION EXPERIMENTS

For comparison we have included the results obtained with five patients. They were fasted as a therapeutic measure for epilepsy. The results for the first six days only are presented, as these are what interest us here.

The results are strikingly similar. The blood sugar in all gradually fell, reaching the lowest value on the fourth day, this being about 60 or 70 per cent. of the normal value. The value for the carbon dioxid combining power of the serum showed a remarkable parallelism with the blood sugar, reaching its low value at the same time as the blood sugar. The acetone bodies in the blood and the acetone body excretion increased, showing an inverse relationship to that of the blood sugar and combined carbon dioxid of serum. After the fourth day there was a tendency for the concentration of these substances to return to a more normal value, and to remain at a constant level after the sixth day. Case 2 showed these changes typically, and we will use values obtained from this patient to compare with those of Case 1.

The differences are a matter of degree. While Case 2 showed a drop in blood sugar amounting to about 30 per cent., this low value being reached in four days, Case 1 showed a drop of 50 per cent., reaching the lowest value in two days. In Case 1 the rapidity rather than the extent of the drop in the combined carbon dioxid of serum is noticeable. The excretion of acetone bodies was much less in Case 1 than in the control subject, Case 2 (Table 2), even when allowance is made for this patient's (Case 2) greater weight. This is a rather unexpected result for which no explanation is available. It must be borne in mind, however, that it is a single observation and may not be a regular occurrence.

The nitrogen output of Case 1 showed rather high values from the outset (compare with later values on a known diet) with no

tendency to drop toward the end of the experiment. The control, however, showed a nitrogen excretion which increased up to the third day and thereafter gradually fell.

EXPERIMENTS WITH DIETS WITH HIGH FAT-CARBOHYDRATE RATIO

Experiment 1.—Some time after the observations recorded in the foregoing, Case 1 and a control subject were fed on a diet in which the fat-carbohydrate ratio was gradually increased. The control was a

TABLE 2.—*Fasting Periods. Normal Children*

Case Number, Age	Day of Fast	Weight, Kg.	Blood Sugar, per Cent.	Carbon Dioxid Combining Power of Serum, per Cent. by Volume	Acetone Bodies in Urine	Acetone Bodies in Blood	Creatinin in Urine, Mg.	Total Nitrogen in Urine, Gm.
2	1	17.9	0.110	61.4	....	....	214	4.32
4 yrs.	2	....	0.104	....	2.54	....	194	3.82
	3	....	0.088	....	6.69	....	244	7.19
	4	....	0.085	....	8.82	....	215	5.60
	5	....	.....	33.8	6.75	....	214	5.78
	6	16.0	0.095	35.7	6.07	....	...	....
3	1	18.3	0.111	57.9	....	....	...	....
4 yrs.	2	....	0.082	....	0.08	....	...	....
	3	....	0.070	....	5.39	....	...	....
	4	....	.....	35.3	6.51	1.08	...	....
	5	....	.....	....	5.05	....	...	....
	6	16.8	0.071	39.5	5.25	....	...	....
4	1	37.6	0.126	63.3	....	....	...	....
12 yrs.	2	....	0.103	....	....	0.20	...	....
	3	....	0.086	51.0	....	0.75	...	....
	4	....	0.084	....	....	....	...	....
	5	....	0.084	46.8	....	1.13	...	....
	6	36.8	0.093	....	4.60	0.91	...	....
5	1	....	0.107	65.3	....	....	...	....
12 yrs.	2	....	0.083	52.8	....	0.20	...	....
	3	....	0.077	....	....	....	...	....
	4	....	0.073	43.3	....	1.13	...	....
	5	....	0.076	....	....	....	...	....
	6	....	0.080	50.3	....	0.94	...	....
6	1	....	0.101	....	....	....	...	....
9 yrs.	2	....	0.093	....	0.11	....	...	....
	3	....	0.070	....	1.16	....	...	....
	4	....	0.074	....	1.72	....	...	....
	5	....	.....	....	....	....	...	....
	6	....	0.080	....	....	....	...	....

child, aged 4½ years, who was convalescent from an attack of post-diphtheritic paralysis. In every other respect she was a normal child. The diets were so arranged that each child received about the same number of calories per kilogram of body weight each day (namely, 60), and a fluid intake of 66 c.c. per kilogram of body weight. A protein intake of 1 gm. per kilogram of body weight daily was given, this being considered sufficient for maintaining nitrogen balance under ordinary conditions. The diet consisted of cream, casein (Mead's Casec) and cane sugar. The percentage of fat in the cream given was tested daily by the Babcock method. The protein and carbohydrate of the cream were estimated from tables showing the average percentage

of these in cream of varying fat content. Five diets were given each for a period of two days. With each change in diet the proportion of fat was increased and the carbohydrate lessened, while the protein and caloric intake remained fairly constant. During the last three periods, the control subject refused small portions of her food. Her absolute intake was carefully measured. The diets given are shown in Tables 3

TABLE 3 *(Case 1).—Diet Gradually Increasing in Fat-Carbohydrate Ratio, Beginning April 18, 1922, at 2 P. M.*

				Food Intake, Gm.				Urine			Blood	
Date, 1922	Day	Diet	Weight, Kg.	Fat	Carbohydrates	Protein	Calories	Creatinin, Mg.	Total Nitrogen, Gm.	Acetone Bodies	Sugar, per Cent.	CO_2 Combining Power of Serum
April 18	...	...	....	....	....	....	.....	...	....	....	0.096	68.3
April 18-19	1	I	11.5	54.0	64.8	11.5	818	Specimen incomplete			0.137	....
April 19-20	2	I	11.1	54.0	64.8	11.5	818	Specimen incomplete			0.142	....
April 20-21	3	II	11.1	63.7	26.4	12.0	756	93	1.72* (2.28)	0	0.099	....
April 21-22	4	II	11.1	63.7	26.4	12.0	756	120	2.06	0	0.095	53.6
April 22-23	5	III	11.0	74.0	13.1	11.9	803	116	2.13	0	0.086	52.8
April 23-24	6	III	11.0	74.0	13.1	11.9	803	134	2.48	0.65	0.096	51.9
April 24-25	7	IV	10.9	77.9	10.3	11.8	823	102	1.81	1.84	0.095	53.8
April 25-26	8	IV	11.0	77.9	10.3	11.8	823	132	1.75	0.54	0.085	51.3
April 26-27	9	V	10.9	63.5	9.0	12.1	684	82	1.08* (1.62)	0.71* (1.07)	0.087	51.9
April 27-28	10	V	10.8	63.5	9.0	12.1	684	139	2.21	1.13	0.084	50.0
April 28-29	11	...	10.6	13.6	138.0	11.9	744	115	1.30	0.06	.....	60.5

* This specimen was incomplete, and the values given in parentheses are the values rected on the basis of normal creatinin excretion during the other days of the experiment.

TABLE 4 *(Control).—Diet Gradually Increasing in Fat-Carbohydrate Ratio, Beginning April 18, 1922*

				Food Intake, Gm.				Urine			Blood	
Date, 1922	Day	Diet	Weight, Kg.	Fat	Carbohydrates	Protein	Calories	Creatinin, Mg.	Total Nitrogen, Gm.	Acetone Bodies	Sugar, per Cent.	CO_2 Combining Power of Serum
April 18	...	...	15.0	....	....	....	.....	...	....	....	0.112	58.9
April 18-19	1	I	14.8	68.3	78.6	14.6	1,024	158	2.69	0	0.113	....
April 19-20	2	I	14.7	68.3	78.6	14.6	1.024	164	2.41	0	.....	....
April 20-21	3	II	14.8	79.9	32.3	15.0	945	153	2.38	0	0.117	....
April 21-22	4	II	14.7	79.9	32.3	15.0	945	147	2.60	1.21	0.104	61.4
April 22-23	5	III	14.4	91.3	16.2	14.8	984	151	2.88	5.24	0.116	47.1
April 23-24	6	III	14.4	88.1	15.6	14.3	951	142	2.52	6.24	0.104	44.3
April 24-25	7	IV	14.3	95.9	12.8	14.6	1,009	150	2.74	9.66	0.088	47.5
April 25-26	8	IV	14.4	94.0	12.5	14.3	965	135	2.01	6.67	0.086	43.8
April 26-27	9	V	14.3	75.3	10.1	13.7	805	156	2.58	6.84	0.086	42.4
April 27-28	10	V	14.1	83.7	11.2	15.2	896	158	2.38	7.51	0.091	48.1
April 28-29	11	...	14.5	17.2	160.0	15.1	925	185	1.88	1.16	.....	61.4

and 4. We have measured the ketogenic and antiketogenic factors in these diets according to the data provided by Schaffer and Woodyatt. Without giving the details of this calculation, it was found that Diet 4 (that given on the seventh and eighth days) showed the greater *ketogenic-antiketogenic* ratio. Using Schaffer's data ketosis should not have appeared until Diet 4 was given and should have disappeared on Diet 5, while with Woodyatt's formula ketosis would be likely to develop in Diet 2 (third and fourth day). The main object of this

experiment was to ascertain whether a ketosis produced by diet would cause symptoms of recurrent vomiting in the patient or changes in metabolism differing from a normal control. Tables 3 and 4 give the results of this experiment.

Both patients took the diet well except for a slight anorexia on the part of the control. The food which she refused was not enough, however, to interfere with the results. They both lost weight slightly but otherwise remained well. On examining the tables, we note the following facts. The nitrogen excretion in the urine remained nearly constant throughout. In both cases there was a slight negative balance in nitrogen, somewhat more marked in the control. The nitrogen output in the stools was not determined, but as each patient had only one small bowel movement throughout the period the error thereby introduced is not large.

The acetone body excretion showed an unexpected result. The control subject was the first to show acetone bodies in the urine, namely, on the fourth day, whereas L. S. did not show these until the sixth day. In addition, the control showed a much higher excretion of acetone bodies than L. S. They both reached their highest level on the seventh day (i. e., the first day of the diet in which the fat-carbohydrate ratio was greatest).

The blood sugar in both cases dropped slightly as the fat-carbohydrate ratio was increased. In L. S. on the second and third day abnormally high values for blood sugar were obtained which we are at a loss to explain. His normal level must actually be taken as 0.10 per cent., which was the first value in this experiment and the normal value in the other experiments.

The combined carbon dioxid of the serum showed some difference between the patient and the control. The first value of 68.3 per cent. by volume in L. S. is abnormal, and we feel justified in using 60 per cent. by volume as his normal level in drawing our conclusions, as this was the normal value obtained in all of his other experiments. The drop in the combined carbon dioxid of the serum in L. S. was slight, in the control it was definitely greater. This corresponds with the much greater ketosis which the control showed. It has recently been shown by Gamble, Ross and Tisdall [5] that the reduction of serum bicarbonate in ketosis is due entirely to an increase in the concentration of the ketone acids in the serum. Therefore, the degree of reduction of the serum bicarbonate is a measure of the ketosis. As might be expected, the return to a high carbohydrate diet on the eleventh day caused a return of the blood and urine findings to normal.

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5. Gamble, Ross and Tisdall: Transactions of the Thirty-Fourth Annual Meeting of the American Pediatric Society.

Experiment 2.—A second investigation on L. S. was made with high fat-carbohydrate ratio in the diet. This was of a different nature. It was an attempt to find out whether a sudden change to a high fat diet would produce results different from those in the preceding experiment. In order to make these results comparable he was placed immediately on a diet similar to Diet 5 of the preceding experiment. The findings are recorded in Table 5.

After being placed on the high fat diet no change occurred in the child's condition for nearly twenty-four hours. He then became drowsy and his breath smelled of acetone. He remained drowsy during the three days that he was taking this diet. He took food well without vomiting. The following points are of interest in examination of Table 5. When the high fat diet was begun the nitrogen excretion rose suddenly to a high level and then dropped gradually. The acetone body

TABLE 5 *(Case 1).—Diet Abruptly Increasing in Fat-Carbohydrate Ratio, Beginning May 9, 1922*

				Food Intake, Gm.				Urine			Blood	
Date, 1922	Day	Diet	Weight, Kg.	Fat	Carbohydrates	Protein	Calories	Creatinin, Mg.	Total Nitrogen, Gm.	Acetone Bodies	Sugar, per Cent.	CO_2 Combining Power of Serum
May 10-11	...	#	11.7	13.6	140.0	11.9	750	147	....	0	0.105	....
May 11-12	2	#	11.1	13.6	140.0	11.9	750	144	2.18	0	0.112	60.7
May 12-13	3	V	11.0	63.5	9.0	11.9	688	59	*1.65 (3.96)	*0.16 (9.38)	0.069	....
May 13-14	4	V	10.9	64.0	9.0	11.9	688	161	3.50	1.55	0.062	41.7
May 14-15	5	V	11.4	64.0	9.0	11.9	688	117	2.63	1.23	0.069	44.7
May 15-16	6	#	11.4	13.6	140.0	11.9	750	140	2.18	0.35	.....	....

* This specimen was incomplete, and the values given in parentheses are the values corrected on the basis of normal creatinin excretion during the other days of the experiment.
\# High carbohydrate diet.

excretion was slightly higher than in the preceding experiment. The blood sugar and combined carbon dioxid of serum showed a sudden drop comparable to that seen in the starvation period, and much greater than on the same diet in the preceding experiment. They both showed a tendency to return to higher values by the third day of the experiment.

COMMENT

The most striking features in connection with this patient (Case 1) are that he had repeated attacks of vomiting and convulsions. These were coincident with fever when he took practically no food, and occurred once when he was merely deprived of food. Deprivation of food did not invariably produce vomiting, for, on two occasions, starvation was not followed by this symptom.

In one spontaneous attack the blood sugar was reduced to 0.037 per cent. During two periods of artificial starvation his blood sugar

was determined, and was found to fall more rapidly than did that of several children who served as controls. He seemed to be unable to meet immediately the demand for carbohydrate produced by its complete withdrawal from the diet. Since normally this emergency is met by a utilization of the carbohydrate reserve, we might conclude, as Hilliger did in 1914 from a study of a similar patient, that L. S. was unable to use his carbohydrate reserve on such an occasion. There is, however, another possible explanation, namely, that L. S., instead of being unable to use his carbohydrate reserve in an emergency, used it up very rapidly at the beginning. In either case, after the first few hours, the result would be the same, i. e., there would be no available carbohydrate reserve to draw on and under the conditions of sufficiently complete, sufficiently sudden, and sufficiently prolonged withdrawal of carbohydrate, changes in metabolism such as we have described, a rapid drop in blood sugar and a rapid rise in acetone body production, would develop. We simply offer this hypothesis as an alternative to that of Hilliger, reserving comment until we have studied the condition further in other children.

All who write on recurrent vomiting lay stress on the occurrence of fever in an attack, some to such an extent that they believe the attack to have its basis in an infection. On considering the history of our patient, one cannot but be struck by the frequency of infection at the onset of the attacks. In the first attack there was otitis media, in the second a high fever of unexplained origin, in the third rhinopharyngitis, and in the fourth possibly otitis media. Infections in children are frequently accompanied by acetonuria, the cause of which may be found partly in the anorexia that accompanies infections and partly in the increased metabolism of infection. An increased demand for carbohydrate dependent on the increased metabolism, and a sufficiently complete and prolonged withdrawal of the supply of carbohydrate, dependent on the anorexia, might easily be the factors which determine the onset of an attack, in a child unable, as was L. S., to meet such an emergency. This of course is pure conjecture and we have no experimental evidence to support it.

Attacks of recurrent vomiting are frequent following general anesthesia, or in conditions involving excitement, fright, or nervousness and occur in children who might be described as highly strung. Until more exact data are available in these conditions with regard to the changes in metabolism, especially of carbohydrates, it is impossible to say what part, if any, are played by the etiologic factors that are at work in Case 1. It is true that usually, at the time of an operation, there is a period of starvation that might conceivably precipitate an attack, but this is not entirely satisfactory and undoubtedly there are

other factors at work which are at present too obscure to admit of discussion, such as rapidity of oxidation of glucose under these conditions, availability of carbohydrate reserves, and others.

It has been abundantly shown that withdrawal of carbohydrates to a point where ketosis may occur is accompanied by a rise in protein catabolism. That this rise in protein catabolism may be one of the factors in the defense against the changes in metabolism brought on by a sudden withdrawal of carbohydrate, as shown by L. S., is suggested by a comparison of the two fat-feeding experiments. The ketone body excretion in the two experiments was very nearly the same, but both the blood sugar and combined carbon dioxid of the serum dropped much lower in the second experiment in which the high fat low carbohydrate diet was suddenly introduced. In his experiment the nitrogen excretion rose considerably on the first day, and then gradually fell. This is in striking contrast to the nitrogen excretion during the first experiment where the fat in the diet was gradually increased. In that case the nitrogen excretion showed no appreciable increase. With the gradual fall of the nitrogen excretion on the second and third days of the second experiment the combined carbon dioxid of serum, and the blood sugar, rose slightly. The rise in nitrogen excretion in the first three days of fasting in Case 2 is likewise evidence of the increased catabolism of protein when there is a sudden increased need for antiketogenic factors.

Hilliger, in his studies on the metabolism of a patient similar to ours, supposed that there was no lack of carbohydrate in the organism, but that some deficiency in the function of the adrenals prevented the formation of a substance that stimulated the mobilization of glycogen. We gave L. S. epinephrin subcutaneously during a normal period and during an attack. During the normal period he showed a marked rise in blood sugar, while during an attack the rise was very slight, from 0.045 to 0.055 per cent.

Recent work has demonstrated that there is a group of symptoms associated with low blood sugar. Banting, Macleod and their collaborators found that rabbits under the influence of insulin regularly develop convulsions when the blood sugar reaches a value of 0.045 per cent. or less, and that glucose relieves these symptoms with great rapidity. Diabetic patients under the influence of too large a dose of insulin, become irrational, comatose, and occasionally have muscular twitchings, and these symptoms are associated with a very low percentage of sugar in the blood. In the light of these facts the convulsions which L. S. had during several of his attacks have considerable significance. Marfan mentions convulsions as occasionally occurring in severe attacks of recurrent vomiting, often at the onset, and as occasionally replacing the vomiting attacks. Two of the patients who came to this

clinic recently gave histories of convulsions, in fact one of them was brought to the hospital after an attack of recurrent vomiting which had been ushered in by a general convulsion.

One more fact brought to light by these studies is the specific effect of glucose in bringing the attacks to an end in L. S. The effect was striking, even when a very small amount (10 gm.) was given by mouth in a single dose. With other patients who were not studied from the point of view of blood sugar, the effect of glucose has not always been so regular or so striking even when given in larger doses.

SUMMARY

The outstanding features in the clinical history of L. S. were recurrent attacks of vomiting during which he excreted acetone bodies, became drowsy, at times showed signs of acidosis and occasionally had convulsions. The only one of these attacks which we studied showed certain changes in the blood which we were able to reproduce artificially by a sudden, but not by a gradual, withdrawal of carbohydrate. The changes which we found were the rapid lowering of the blood sugar and carbon dioxid combining power of the blood. At the same time there was an early appearance of acetone bodies in the urine. During one attack the blood sugar was found to be greatly reduced. We believe that hypoglycemia was probably an essential factor in these attacks. It is probable that many attacks of recurrent vomiting are of the same nature as those of our patient, especially those attacks occurring with fever. Such hypoglycemia cannot be detected, unless the determination is made at the height of an attack, for recovery is very rapid. The convulsions of our patient, and the fact that they are at times to be obtained from the histories of other patients lends strong support to the view that hypoglycemia is the determining factor in at least some of the attacks.

THE VOLUME INDEX AND COLOR INDEX OF THE RED BLOOD CORPUSCLES IN NEW-BORN INFANTS *

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Numerous studies of the blood of new-born infants have established the fact that the red corpuscles and hemoglobin are much higher during this period than in adult life. The figures given by different observers vary, however, quite widely. This variation is especially striking in the hemoglobin determinations.

Lippman [1] has recently completely summarized the literature on the blood during the new-born period. He adds the results of his own study of the blood of seventy-one infants during the first 48 hours of life. This observer found the average red cell count at birth to be 5.2 million per cubic millimeter. At the end of six hours the average count had risen to 5.65 million, the increase being due seemingly to greater activity of the hemopoietic organs. At eighteen hours the count had fallen to 5.4 million, at which point it remained for the rest of the forty-eight hour period.

The hemoglobin estimations reported in the literature are usually given in per cent. The widely varying results of different workers are due largely to the frequent use of methods which are technically inaccurate, and to the lack of common agreement as to what 100 per cent. shall mean. It is apparent that percentages mean nothing unless the absolute figure, to which the 100 per cent. on the scale used is equivalent, be known. Williamson,[2] using the accurate spectrophotometric method of hemoglobin estimation, found the hemoglobin on the first day of life to be 23.25 gm. per hundred cubic centimeters and 22.12 gm. per hundred cubic centimeters for the fourth to eighth day. The average for men in adult life he found to be 16.92 gm. per hundred cubic centimeters, hence on this standard the figure for the first day is equivalent to 137 per cent. The figures of Williamson are, in fact, the only absolute and accurate figures available for comparison.

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* Received for publication, Aug. 6, 1924.

* From the University of Kansas Medical School.

1. Lippman, H. S.: A Morphologic and Quantitative Study of the Blood Corpuscles in the New-Born Period, Am. J. Dis. Child. **27**:473 (May) 1924.

2. Williamson, C. S.: Influence of Age and Sex on Hemoglobin. A Spectrophotometric Analysis of Nine Hundred and Nineteen Cases, Arch. Int. Med. **18**:505 (Oct.) 1916.

Since the color index is the relation of the number of red cells to the hemoglobin content, one readily sees that no accurate determinations are possible with the varying and unreliable hemoglobin determinations. Williamson did no red cell counts. For a color index the cell count and hemoglobin determination should be done simultaneously. Mayers,[3] for instance, has attempted to calculate color indexes from his red cell counts and Williamson's hemoglobin estimations for the same age. Conclusions from such determinations are impossible. Lucas [4] has done simultaneous red cell counts and hemoglobin estimations. A calculation of the color index from his data would be impossible also, since he does not state the standard to which the 100 per cent. on his scale is equivalent. His hemoglobin determinations were done by the acid hematin method. In the results, the red cell counts correspond closely with the hemoglobin estimations.

The color index of the red cells is dependent on the volume of the red cell and hemoglobin concentration within the cells. The volume factor has been largely overlooked. One of us [5] has pointed out methods by which these factors can be accurately and absolutely estimated. We have shown that with such methods the red cells of normal adults show a uniform volume and hemoglobin content, and that the color index is always 1.00. A low color index in anemia may be due to a decrease in hemoglobin content or to a combined decrease in hemoglobin content and cell volume. On the other hand, a plus color index always means an increased cell volume, since supersaturation of cells by hemoglobin never occurs. These conclusions are based on a study of 171 persons, including many normal persons, and on patients with different types of anemia.

The best measure of cell volume is the volume index of Capps.[6] This expresses the volume of the red cell relative to normal. It is calculated by dividing the mass of red cells in percentage of normal by the number percentage of cells. It is analagous to the color index in expressing the average cell volume instead of the average hemoglobin content as does the color index.

We have determined the mass of the red cells by the technic suggested by Hooper, Smith, Belt and Whipple.[7] Ten cubic centimeters of blood is withdrawn by venipuncture and run into a centrifuge tube containing 2 c.c. of 1.6 per cent. sodium oxalate, an isotonic anticoagu-

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3. Mayers, L. H.: A Study of the Erythrocyte Curve at Various Ages and Its Relationship to Hemoglobin Curve, Arch. Int. Med. **30**:478 (Oct.) 1922.
4. Lucas, W. P., et al.: Blood Studies in the New-Born, Am. J. Dis. Child. **22**:525 (Dec.) 1921.
5. Haden, R. L.: Accurate Criteria for Differentiating Anemias, Arch. Int. Med. **31**:766 (May) 1923.
6. Capps, J. A.: J. M. Res. **5**:367, 1903.
7. Hooper, C. W.; Smith, H. P.; Belt, A. E., and Whipple, G. H.: Am. J. Physiol. **51**:205 (March) 1920.

lant. The tube is contrifuged for one-half hour. The true cell mass is thus obtained without changes due to shrinking or swelling of the cells.

The red cell counts have all been done on oxalated blood withdrawn by venipuncture. Usually duplicate counts have been made, using only pipets and counting chambers certified as correct by the United States Bureau of Standards. The hemoglobin has been determined on the same oxalate blood, using the ferricyanid method of Haldane as Van Slyke [8] adapted to his blood gas apparatus and is calculated directly in grams. In determining the percentage of hemoglobin, 15.6 gm. per hundred cubic centimeters of blood has been taken as 100 per cent., since one of us has found this figure to be the average hemoglobin content of normal adult blood with a count of 5,000,000 per cm., which is reckoned as 100 per cent. of cells.[9]

The data thus obtained afford an exceedingly accurate basis for the calculation of the volume index and color index. Since the color index indicates only the amount of hemoglobin to each cell and not the concentration, one of us (R. L. H) has suggested a third index, which indicates directly the hemoglobin content per unit volume compared with normal.[5] This index has been called the "saturation index." The saturation index is calculated by dividing the hemoglobin percentage by the percentage by volume of cells. From this data we can also figure the actual volume and hemoglobin content of the average cell as well as the hemoglobin content of the cell mass.

The details of the calculation of the three indexes as determined here can best be illustrated by an example. On centrifuging 10 c.c. of an unknown blood with 2 c.c. of oxalate solution, 2.4 c.c. of packed corpuscles are obtained. Ten cubic centimeters of normal blood containing five million corpuscles per cm., when similarly centrifuged yields 4.8 c.c. of packed cells (International No. 2 centrifuge). The volume by percentage of cells in terms of normal is $\frac{2.4}{4.8}$ or 50 per cent. The count of the red blood cells of the unknown blood is three million or 60 per cent. of normal. Normal blood contains 15.6 gm. of hemoglobin per hundred cubic centimeters. The unknown blood is found to contain 6.24 gm. which is $\frac{6.24}{15.6}$ or 40 per cent. of normal. In this blood the volume of the average cell is 83 per cent. of normal, the average cell contains 67 per cent. of the normal amount of hemoglobin, and the protoplasm of the cells is 80 per cent. saturated with hemoglobin.

Most of the observations on the blood of the new-born have been made on peripheral blood. Lucas [4] made red cell counts and hemoglobin determinations on both sinus and peripheral blood. He found the aver-

8. Van Slyke, D. D.: J. Biol. Chem. **33**:31, 1918; ibid. **49**:1 (Nov.) 1921.
9. Haden, R. L.: The Normal Hemoglobin Standard, J. A. M. A. **79**:1496 (Oct. 28) 1922.

age hemoglobin and cells higher in the peripheral than in the sinus blood. He reports only the average for different age intervals and not the results in individual cases. We have made all determinations on blood obtained from the longitudinal sinus. Determinations were taken only on normal children. In six infants, simultaneous counts were done on blood obtained by pricking the heel.

The results of our study of the sinus blood of eleven infants are summarized in Table 2. The red cell counts vary from 3.40 to 4.57 millions, with an average of 3.96 millions. The hemoglobin varies from 14.4 gm. per hundred cubic centimeters to 20.1 gm. per hundred

TABLE 1.—*Volume, Color and Saturation Index*

The volume index:	$\frac{\text{volume percentage of cells}}{\text{number percentage of cells}}$	$= \frac{50}{60} =$	0.83
The color index:	$\frac{\text{hemoglobin percentage}}{\text{number percentage of cells}}$	$= \frac{40}{60} =$	0.67
The saturation index:	$\frac{\text{hemoglobin percentage}}{\text{volume percentage of cells}}$	$= \frac{40}{50} =$	0.80

TABLE 2.—*Findings in Sinus Blood*

Age	Red Blood Count in Millions per C.Mm.	Volume per Cent. Red Blood Count	Gm. Hemoglobin per 100 C.c.	Hemoglobin in per Cent.	Volume Index	Color Index	Saturation Index
11 hours	4.57	104	15.6	100	1.10	1.14	1.04
5 days	3.52	115	17.8	114	1.64	1.63	1.00
5 days	3.86	106	16.2	104	1.38	1.35	0.98
5 days	4.21	133	20.1	129	1.58	1.53	0.97
6 days	4.50	119	18.8	120	1.32	1.33	1.00
8 days	4.22	104	16.4	105	1.24	1.25	1.01
9 days	4.12	121	18.5	119	1.47	1.45	0.98
9 days	3.87	123	19.2	123	1.56	1.56	1.00
9 days	3.81	112	16.6	107	1.47	1.41	0.96
13 days	3.69	110	17.4	112	1.48	1.51	1.02
24 days	3.40	90	14.4	92	1.32	1.35	1.02
Average	3.96	113	17.37	112	1.43	1.41	0.99

cubic centimeters. The average is 17.37 gm. On the normal adult standard scale these figures are equivalent to 92 per cent. for the lowest, 129 per cent. for the highest and 112 per cent. for the average. The percentage by volume of cells runs close to the hemoglobin in percentage, the lowest being 90 per cent. of normal, the highest 133 per cent. and the average 113 per cent. The cell volume is an excellent check on the accuracy of the hemoglobin determinations.

The color index and volume index are high in every case. The maximum volume index is 1.64, the minimum 1.10 and the average 1.43. The maximum color index is 1.63, minimum 1.14 and average 1.41. The saturation index shows little variation from normal, running from 0.96 to 1.04. The average is 0.99. The concentration of hemoglobin

per unit volume of cells is thus normal. These figures show that the changes observed are all dependent on an increased volume of the average red cells in the new-born.

In several cases blood films were studied. No nucleated red cells were found. There was no anisocytosis or poikilocytosis. The greater cell volume is due to a uniform increase in diameter and thickness.

From the absolute data obtained by the methods employed here we can calculate the actual volume and hemoglobin content of the average cells and the hemoglobin percentage within the cell mass. The figures for five cases, the average for the eleven cases, as contrasted with the normal for adult blood are shown in Table 3. The volume of the

TABLE 3.—*Comparison of Red Cell Count in Sinus and Peripheral Blood*

	Red Cells in Millions	
Age, Days	Sinus	Peripheral
5	3.52	6.23
5	3.86	5.94
9	3.87	5.09
9	3.81	4.34
13	3.69	3.58
24	3.40	4.08

TABLE 4.—*The Volume and Hemoglobin Content of the Average Individual Cell of the New-Born Compared with the Normal Adult*

Red Blood Count in Millions	Volume per Cent. of Cells	Hemoglobin in per Cent.	Volume of Average Cell in C.c. by 10^{-11}	Gm. Hemoglobin in Average All by 10^{-11}	Actual Percentage of Hemoglobin in Cell	Remarks
4.57	104	100	10.6	3.6	31.2	Age 11 hours
3.52	115	114	15.7	5.1	32.5	Age 5 days
4.50	119	120	12.7	4.1	32.5	Age 6 days
4.12	121	119	14.1	4.6	32.6	Age 9 days
3.69	110	112	14.1	4.6	32.6	Age 13 days
3.96	113	112	13.7	4.38	32.0	Average 11 new-born
4.74	95	95	9.6	3.12	32.5	Aver. 52 normal adults

average cell is 13.7 x 10^{-11} c.c. contrasted with the normal adult average of 9.6 x 10^{-11}. The grams of hemoglobin in the average cell is 4.38 x 10^{-11}, while the normal adult average is 3.12 x 10^{-11} gm. The actual percentage of hemoglobin in the cells is practically the same, 32.0 per cent. for the new-born and 32.5 per cent. for the adult.

The figures for the six cases in which red cell counts were done on both sinus and peripheral blood are shown in Table 4. The peripheral blood was obtained by pricking the heel immediately after the blood had been withdrawn from the sinus. In each instance the same pipet was used in diluting the blood from the two sources. The counts are uniformly higher in the peripheral than in the sinus blood. The higher count in peripheral blood is probably related in some way to the increased individual cell volume, which might cause a stagnation of the cells in the capillaries. In pernicious anemia the fundamental and most charac-

teristic change in the blood is the increase in the volume of the average cell. Duke [10] and Stofer have pointed out in this disease that the cell counts are often higher in peripheral than in venous blood.

We have not studied the blood of older children to determine just when the red blood cell reaches the average normal adult. In one infant, aged 3 months, however, the volume and color index were 1.00.

SUMMARY

A study of the red cell count, cell mass, and hemoglobin content of the blood from the longitudinal sinus of eleven normal infants under 24 days of age is presented.

The average red cell count is 3.96 millions per c.mm., and the cell mass 112 per cent. of the adult normal. The average hemoglobin is 17.37 gm. per hundred cubic centimeters, which is equivalent to 113 per cent. taking 15.6 gm. per hundred cubic centimeters as 100 per cent.

The volume index and color index are high in every case.

The volume index ranges from 1.10 to 1.64, the color index from 1.14 to 1.63.

The saturation index is approximately normal, the average being 0.99. This shows that the actual percentage of hemoglobin per unit volume of cell is the same as in the adult.

No quantitative changes were observed in the red cells, but there was a uniform increase in volume.

Simultaneous counts in sinus and peripheral blood show usually a higher count in the peripheral blood than in the sinus blood.

The most desirable standard to use in hemoglobin determinations in the new-born is the normal adult standard, namely, 15.6 gm. per hundred cubic centimeters of blood as 100 per cent.

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10. Duke, W. W.: Specific Tests in the Diagnosis of Allergy, Arch. Int. Med. **32**:298 (Aug.) 1923.

IMMUNITY RESULTS OBTAINED WITH DIPHTHERIA TOXOID (MODIFIED TOXIN) AND ONE-TENTH L + MIXTURES OF TOXIN-ANTITOXIN IN THE PUBLIC SCHOOLS OF NEW YORK CITY (MANHATTAN AND THE BRONX) *

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INTRODUCTION

The large and increasing use of subcutaneous injections of some form of modified toxin for purposes of active immunization, makes it important to utilize this toxin in the form in which it will produce the greatest amount of immunity, with the minimum amount of deleterious after effect. It is important to grasp that in any preparation it is the diphtheria toxin or derivatives of it, and nothing else, that immunizes. Ehrlich, in 1895, discovered that when fresh diphtheria toxin deteriorates in strength a peculiar change takes place. The toxicity for the guinea-pig drops faster than its power to neutralize antitoxin. At a certain stage in deterioration the toxin in even large doses no longer causes death in animals, but it still neutralizes a considerable percentage of its original amount of antitoxin. Thus, if the preparation drops in toxicity from 100 minimum lethal dosage to 5 minimum lethal dosage per cubic centimeter, the original power to neutralize 1.0 unit of antitoxin still holds to the extent of neutralizing 0.1 of a unit; that is, while the toxicity has diminished to one-half of 1 per cent., the combining power has diminished only to 10 per cent.

Before Ehrlich had finished his researches, von Behring had already used this deteriorated toxin in his first experiments on the production of antitoxin. He utilized the addition of a small percentage of iodin tetrachlorid (1 : 500) to change the toxin so that he could immunize the animals safely. A little later it was discovered that by adding an amount of antitoxin to the toxin which would neutralize, or nearly neutralize, its toxicity in animals, its immunizing power still remained. The first modification of the toxin is called toxoid, the second toxin-antitoxin. While both of these modifications of toxin continued to be used in

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the immunization of animals, attention was concentrated more on the toxin-antitoxin, and it thus was the first to be used in the immunization of man. Thus it was that von Behring used it in his injections on human subjects.

When we began the work in New York, we also utilized a preparation of toxin-antitoxin because we were familiar with it. At first it was our view that a large amount of toxin almost completely neutralized would be more effective than a smaller amount less nearly neutralized. We therefore utilized a toxin-antitoxin containing in each dose 3 L+ (120 minimum lethal dosage) of toxin and 3½ units of antitoxin. The immunizing results were satisfactory, but the local inflammatory reaction was occasionally severe in those sensitive to the nonspecific substances. We [1] tried a preparation having nearly double the amount of toxin. This, to our surprise, gave no better results.

COMPARISON BETWEEN OLD AND NEW TYPE MIXTURES OF TOXIN-ANTITOXIN

Table 1 shows that mixtures with the larger number of L+ doses were not more efficient than those with the smaller number of L+ doses, so long as the mixtures were equally toxic (under-neutralized). In fact, we noted that mixtures with the smaller number of L+ doses

TABLE 1.—*Comparison Between Different Mixtures of Toxin-Antitoxin Varying in Toxicity and Number of L+ Doses Per Cubic Centimeter (Zingher)*

		Action on Guinea-Pig (Tests by Banzhaf)		Results in Children				
Mixture	Composition of Toxin Antitoxin Mixture	Amount Injected, C.c.	Result	Number Doses	Amount of Each Dose, C.c.	Total Number Schick Retested	Schick Negative	Per Cent. Negative
41	6 L doses of toxin and 7 units of antitoxin	1.0	Partial paralysis in 16 days; recovery	3	1.0	985	570	57.8
		5.0	Paralysis; death in 15 days					
42	5 L doses of toxin and 5.8 units of antitoxin	0.5	Paralysis; death in 17 to 20 days	3	1.0	3,846	3,356	87.3
		1.0	Paralysis; death in 17 days					
		5.0	Death in 3 days					
43	3 L doses of toxin and 5.8 units of antitoxin	1.0	Paralysis in 16 days; recovery	3	1.0	142	137	95.9
		3.0	Paralysis; death in 17 days					
		5.0	Death in 3 days					

per cubic centimeter, but showing greater toxicity for the guinea-pig, gave better immunity results than those with the larger number, which were more neutralized. This led one of us (P.) to make use of preparations containing less toxin and finally one containing but one-thirtieth of the amount of toxin, or 0.1 L+ and 0.75 unit of antitoxin was

1. Zingher, A.: Active Immunization with New Mixture (1/10 L) of Toxin-Antitoxin in Public Schools of New York City (Manhattan and Bronx), New York State J. M. **24**:49-56 (Feb. 1) 1924.

adopted. The results were as satisfactory as with the older preparation, and the local reaction was much less. This has become the standard preparation in this country.

TABLE 2.—*The Antitoxin Development Produced by Three Injections of Mixtures* Having Different Amounts of Toxin Partially Neutralized by Antitoxin (Schroder)*

Amount of Original Toxin in 1 C.c. of Mixture	Number of Children Receiving Three Injections	Per Cent. of Nonimmunes Shown to Be Immune on Schick Retest Four Months Later
0.1 L (4 lethal doses)	490	90
0.5 L (20 lethal doses)	304	95
3.0 L (120 lethal doses)	318	92
5.0 L (200 lethal doses)	487	85

* All mixtures caused severe paralysis in guinea-pigs, followed usually by death in eighteen days among those animals that received 1 c.c.; with 5 c.c. doses, death followed in ten days.

Table 2 shows the antitoxin development after three injections of mixtures having different amounts of toxin and all partially, but equally, neutralized by antitoxin.

TABLE 3.—*Comparison of Results with Different Mixtures of Toxin-Antitoxin Containing from One-Tenth to One-Twentieth L + Per Cubic Centimeter Relation Between Action on Guinea-Pig and Immunizing Efficiency in Children (Zingher)*

			Action on Guinea-Pig (Tests by Banzhaf)		Results in Children				
Mixture	Number L+ in Each C.c.	Number M.L.D. in Each C.c.	Amount Injected, C.c.	Result	Number Doses	Amount, C.c.	Total Number Schick Retested	Schick Negative	Per Cent. Negative
69	1/10	4	1.0	Partial paralysis; recovery	3	1.0	221	213	96.4
			3.0	Paralysis; death in 25 days					
			5.0	Death in 4 days					
65	1/10	4	1.0	Death in 8 days	3	1.0	900	814	94.0
			5.0	Death in 6 days					
67	1/10	4	1.0	Paralysis; death in 22 days	3	1.0	61	53	86.9
			3.0	Death in 9 days					
			5.0	Death in 3 days					
52	1/10	4	2.0	Paralysis in 21 days; recovery	3	1.0	384	342	89.0
			3.0	Paralysis in 17 days; recovery					
			5.0	Paralysis in 17 days; recovery					
70	1/10	4	1.0	Partial paralysis; recovery	3	1.0	55	48	87.4
			3.0	Paralysis; recovery					
			5.0	Paralysis; death in 21 days					
53	1/10	4	1.0	Paralysis; death in 21 days	3	0.5	28	24	85.7
			3.0	Death in 3-5 days	3	0.25	31	24	77.4
			5.0	Death in 3-5 days					
56	1/20	2	1.0	No local effect; no paralysis; recovery	3	1.0	165	97	59.4
			3.0	Paralysis in 21 days; death in 35 days					

Table 3 shows the mixtures used, the effect of varying doses on guinea-pigs, and the immunity results in children. It is interesting to note the high percentage of children who became immune with mixtures

69 and 65. The number of retested children is sufficiently large to be representative, and thus avoid the error so frequently associated with small numbers in diphtheria immunity work.

LOCAL AND CONSTITUTIONAL REACTIONS PRODUCED BY NEW AND OLD TYPE MIXTURES OF TOXIN-ANTITOXIN

The local and constitutional reactions obtained with mixtures of toxin-antitoxin are due to two different substances in the mixtures.

(*a*) In the old type mixtures, containing from 3 to 6 L + doses of toxin per cubic centimeter, there was a considerable amount of autolyzed bacillary substance and other kinds of protein derived from the broth culture itself, which gave rise in sensitive persons to the most marked forms of local and constitutional reactions. These reactions were of an anaphylactic type and generally occurred in hypersensitive persons, who had given a negative pseudo reaction or positive combined reaction. Both the local and constitutional reactions reached their height within twenty-four hours, gradually disappeared in from two to three days, although they persisted at times for from four to six days. The local reaction varied from an area of redness and induration the size of a fifty cent piece to an extensive infiltration involving one-half, or more, of the arm. There was pain, tenderness and slight glandular enlargement in the axilla. Fever was present, the temperature ranging from 100 to 104 F. A few of the persons showing simple positive Schick reactions also had slight local and constitutional disturbances, but the more marked reactions to the toxin-antitoxin were only found in those who had shown themselves to be hypersensitive to the proteins of the mixture by their negative pseudo reactions or positive combined reactions.

(*b*) With the new type of mixture (one-tenth L +) the local and constitutional effects due to the reacting protein were to a large extent eliminated, but the local effect of the larger amount of free toxin present in some of these preparations became more evident. We noticed, following the subcutaneous injections, especially with mixtures of which 1 c.c. caused death of the guinea-pig in from six to eight days and 3 c.c. in from three to five days, local reactions that were slow in appearing, but much more lasting than the protein reactions. These reactions were characterized by local induration and redness, which gradually faded into a brownish-red area of discoloration. The area had a dry, wrinkled, desquamating appearance and resembled on inspection a large positive Schick reaction. With one of these mixtures we even noticed in a few children a superficial necrosis of the skin. This local reaction was due to a large extent to the free toxic fraction of the mixture.

The majority of the mixtures of toxin-antitoxin used in the schools were less toxic, and corresponded more to the degree of underneutralization given for a standard preparation. With such mixtures the local reactions were only slight and often absent. It was possible, in fact, to inject several hundred school children with these new type mixtures during a day's work without hearing subsequent complaints about sore arms, or the necessity of the children remaining away from school for a day or two. Constitutional symptoms, such as fever, were practically absent. This was noticeable even after injecting the more toxic preparations, and was in striking contrast to the disagreeable effects seen with the 3 to 6 L+ mixtures in from 5 to 20 per cent. of school children.

TABLE 4.—*Local Reaction on Second Day and Immunity Response at the End of Three and One-Half Months from Toxin-Antitoxin, Unmodified Toxin and Toxoid (Schroder)*

Preparation Used	Three Doses of C.c.	Adults Tested	Severity of Local Reaction: Very Marked, per Cent.	Marked, per Cent.	Moderate, per Cent.	Slight, per Cent.	None, per Cent.	Immunity Response After 3½ Mos. Schick Negative, per Cent.
Toxin-antitoxin:								
3.0 L in 1 c.c.	1	261	13	36	22	12	17	87
0.1 L in 1 c.c.	1	117	..	10	20	44	26	83
0.1 L in 1 c.c.	0.5	86	..	8	23	45	24	73
Freshly diluted standard toxin without antitoxin:								
0.15 M.L.D. in 1 c.c. 1st dose	1	29	3.5	24	45	24	3.5	41
0.025 M.L.D. in 1 c.c. 2d and 3d doses	1	29	..	4	8	25	62	
Toxoids (old and much deteriorated toxin)	1	211	..	3	10	37	50	70

IMMUNIZING EFFECT OF DETERIORATED TOXIN

During this investigation with toxin-antitoxin, a test was made of the effect of using the aged toxin[2] from which the toxin-antitoxin mixtures were prepared, in a diluted form, without the addition of antitoxin. The minimum lethal dosage of this toxin had dropped from 0.001 c.c. to 0.01 c.c. This was found, as expected, too irritating to be used in sufficient amount to give a satisfactory result. Some of this diluted toxin was tested after storage and it was found to have largely lost its toxicity and to have become toxoid. One cubic centimeter injected in guinea-pigs caused paralysis but not death. It was thought that it would be of interest to test the immunizing value of this in

2. Shroder, M. C., and Park, W. H.: Comparative Merits of New and Old Preparations of Diphtheria Toxin-Antitoxin; Results of Preliminary Tests with Toxoid, J. A. M. A. **81**:1432-1435 (Oct. 27) 1923.

human beings. Two hundred and eleven adults were given these injections (see Table 4). There was no constitutional disturbance and no very marked reactions. In 50 per cent. there were no reactions whatever. The immunity results were moderately good and 70 per cent. of the formerly Schick positive persons gave a negative Schick reaction.

Equally suggestive of the value of toxoid as a good immunizing agent were the results obtained by Zingher [1] with the old type mixtures (from 3 to 5 L+ doses per cubic centimeter) of toxin-antitoxin. Table 5 indicates that these mixtures did not have their immunizing value impaired to any extent after standing for several months, and losing nearly all their toxicity for the guinea-pig. The slight excess

TABLE 5.—*Results Obtained with Fresh Mixtures as Compared with Older Mixtures of Toxin-Antitoxin Containing from Three to Five L + Toxin Per Cubic Centimeter (Zingher)*

	Number L in Each C.c.	Number M.L.D. in Each C.c.	Action on Guinea-Pig (Tested by Banzhaf)		Results in Children			
Mixture			Amount Injected, C.c.	Result	Number Doses Toxin-antitoxin	Total Number Schick Retested	Schick Negative	Per Cent. Negative
44	..	...	1.0	Death in 6 days	3	1,080	1,047	97.0
Fresh	3	120	5.0	Death in 3 days				
44*	3	120	1.0	Slight local effect; death from pneumonia	3	142	137	96.4
Old	..	...	3.0	Moderate local effect; death in 12 days				
			5.0	Moderate local effect; death in 9 days				
42	5	200	0.5	Paralysis; death in 17-20 days	3	3,846	3,356	87.2
			1.0	Paralysis; death in 17 days				
Fresh	..	...	5.0	Death in 3 days				
42*	5	200	1.0	No local effect; no paralysis, recovery	3	364	361	99.1
			2.0	No local effect; no paralysis, recovery				
Old	..	...	5.0	Slight local effect				

* These mixtures were kept at icebox temperature for seven months.

of free toxin being changed into toxoid, these favorable results indicated that toxoid could give rise to antitoxic antibodies and that it was probably an important factor in active immunization. Dissociation of the neutral mixture of toxin-antitoxin after injection need not be considered of any importance, in view of the poor immunizing value of freshly neutralized or overneutralized mixtures.

IMMUNITY RESULTS OBTAINED WITH TOXOID

The above results suggested that there were possibilities in the toxoid preparation that made it well worth while to submit it to further experimentation. For the time being our attention was mainly centered on the new one-tenth L+ preparation of toxin-antitoxin. The

article of Glenny and Hopkins,[3] on using a toxoid with antitoxin instead of the toxin-antitoxin mixture regularly used, then appeared. A little later O'Brien, of the Burroughs, Wellcome & Company laboratories, in writing to one of us said that they were getting excellent immunity results in animals with toxoid made by the addition of 0.1 per cent. formaldehyd to toxin. He sent some of this preparation to us and asked if we would try it on human beings. Dr. Banzhaf immediately injected it into guinea-pigs and Dr. Sawhill injected a few nurses at Bellevue Hospital. The guinea-pigs, when retested three and four weeks later showed immunizing results as good, but not better, than with the toxin-antitoxin preparation.

Glenny, Pope and Hopkins,[4] in an as yet unpublished communication entitled "Further Notes on Modification of Diphtheria Toxin," state that the amount of formaldehyd necessary to produce a given effect on a batch of toxin depends greatly on the aminonitrogen content. To a toxin of which the van Slyke nitrogen was 2.8 mg. per 10 c.c., 0.1 per cent. of formaldehyd was added; after keeping for twenty-four hours at a temperature of 37 C., an intradermic reaction was no longer obtained if the toxin was diluted more than 250 times. Another toxin, with a van Slyke figure of 19.6 mg., after similar treatment, gave a reaction when diluted 10,000 times; this toxin needed at least 0.3 per cent. formaldehyd to reduce the toxicity to the same level as that reached by adding 0.1 per cent. to the other toxin. In a given toxin the amount of modification produced by a given concentration of formaldehyd depends on the temperature and time of exposure.

After modification of toxin many of the tests for combining power can no longer be made. If sufficiently modified, the toxin no longer kills the guinea-pig and so the L + dose cannot be determined. Even the reacting dose on the guinea-pig's skin can no longer be estimated if the toxin is completely changed into toxoid. To obtain an indication of the combining power of such a modified toxin that is no longer capable of producing symptoms in a guinea-pig, Glenny, Hopkins and Pope have added an excess of antitoxin, and after standing the mixture for a number of hours, determined by titration with toxin the amount of free antitoxin left in the mixture. By making a similar experiment previously with the same toxin, which had not been modified, they were able to draw some interesting and important conclusions, indicated in Table 6.

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3. Glenny, A. T., and Hopkins, B. E.: Diphtheria Toxoid as an Immunizing Agent, Brit. J. Exper. Path. **4**:283-288 (Oct.) 1923.

4. Glenny, A. T.; Hopkins, B. E., and Pope, C. H.: Further Notes on Modifications of Diphtheria Toxin (personal communication).

In Table 6 the number of units combined represents the difference between the number of units of free antitoxin detected in the mixture and the number of units originally added. This number of units they call the total combining power. They found that the total combining power had not been markedly reduced by changing the toxin into toxoid, but that the affinity of the modified toxin for antitoxin had been greatly reduced. This is indicated in parts 2 and 3 of Table 6. Leaving the toxoid in contact with the antitoxin for only four hours, as was done in the case of the unmodified toxin, the total combining power was found to be much less; it required fully forty-eight hours for the complete saturation of the toxoid by antitoxin.

TABLE 6.—*Combining Properties of Toxin and of Modified Toxin for Diphtheria Antitoxin (Glenny, Hopkins and Pope)**

	Combining Time with Antitoxin: Four Hours at Room Temperature				
1. Toxin Not Modified:					
Number of units of antitoxin added to 1 c.c. of toxin	15	20	30	40	50
Number of units detected after four hours	5	8	18	28	38
Number of units combined	10	12	12	12	12
Total combining power, 12 units per c.c.					
	Four Hours at Room Temperature				
2. Toxin Modified:					
Number of units of antitoxin added to 1 c.c. of toxin	15	20	30	40	50
Number of units detected after four hours	10	14	22	31	42
Number of units combined	5	6	8	9	8
	Forty-Eight Hours at Room Temperature				
3. Toxin Modified:					
Number of units of antitoxin added to 1 c.c. of toxin	15	20	30	40	50
Number of units detected after forty-eight hours	6	11	20	29	39
Number of units combined	9	9	10	11	11

* Lo dose of toxin, 0.18 c.c. One c.c. toxin neutralized by 5.5 units of antitoxin. Varying amounts of antitoxin in excess of 5.5 units added and after standing residual antitoxin titrated.

In the absence of the simpler animal test for the combining power of modified toxin, Glenny, Hopkins and Pope suggest the use of the flocculation test of Ramon.[5] By this method it is easy to detect whether the combining power of a toxin has altered during modification. Glenny and Okell[6] have recently proposed the use of the symbol Lf comparable with Lr, Lo, for the amount of toxin equivalent to 1 unit of antitoxin, as determined by flocculation.

Table 7 shows the effect of exposing a toxin to various concentrations of formaldehyd at a temperature of 37 C. for twenty-four hours. The flocculating doses recorded in the last column show that the total combining power of the toxin had not been greatly reduced, but that some

5. Ramon, G.: Flocculation in Toxin-Antitoxin Mixtures, Ann. de l'Inst. Pasteur **37**:1001-1011 (Dec.) 1923; ibid. **38**:1, 1924; Compt. rend. Soc. de biol. **86**:661, 1922; ibid. **86**:711, 1922; ibid. **86**:813, 1923; ibid. **89**:2, 1923.

6. Glenny, A. T., and Okell: J. Exper. Path. & Bacteriol. **27**:187 (April) 1924.

TABLE 7.—*Showing the Effect on a Batch of Different Toxins of Treatment with Varying Concentrations of Formaldehyd at a Temperature of 37 C. for Twenty-Four Hours (Glenny, Hopkins and Pope)*

Key Number	Percentage Formaldehyd Added, per Cent.	Number of Minimal Reacting Doses per C.c.	Minimal Lethal Dose, C.c.	Lf, C.c.
J. 3488	Nil	500,000	0.002	0.11
Px 146	0.01	260,000	0.003	0.11
Px 147	0.03	150,000	0.01	0.11
Px 148	0.1	25,000	0.02	0.11
Px 149	0.2	5,000	0.05	0.12
Px 150	0.3	1,200	0.1	0.12
Px 151	0.4	50	2.0	0.12
Px 152	0.5	0	Over 5.0	0.12
Px 153	1.0	0	Over 5.0	0.12

loss had occurred. This could indicate that during the process of conversion of toxin into toxoid either destruction has occurred, or the affinity of the toxoid for antitoxin had been so greatly reduced that even the flocculating value had been affected. The latter is most probably true.

PERSONAL OBSERVATIONS

Several toxoid preparations were made by Banzhaf at the research laboratory according to the English method. These preparations of toxoid were used by Zingher [7] for active immunization on an extensive scale among the school children of New York City. Tables 8 and 9 indicate in a striking way the results noted by him with two different preparations of toxoid.

(*a*) PREPARATION OF TOXOID USED FOR IMMUNIZATION

To each 1,000 c.c. of toxin 1 c.c. of formaldehyd was added. The bottles were shaken up and placed in the incubator, where they were allowed to remain undisturbed at a temperature of 38 C. for from four to five weeks. The preparations were then removed and tested for the minimum lethal dosage and the L+.

(*a*) Toxoid 437 used in the schools, enumerated in Table 8, was made from an old toxin which originally, two years ago, had a minimum lethal dosage of 0.001 c.c. Before the addition of formaledhyd the toxin had a minimum lethal dosage of 0.01 c.c. and an L+ of 0.32 c.c. After the addition of 0.1 per cent. formaldehyd and after remaining in the thermostat for five weeks, the modified toxin was removed, and kept in the icebox until it was standardized and used for immunization.

The minimum lethal dosage of the toxoid was found to be 1.5 c.c. (1 c.c. killed a guinea-pig in thirteen days) and the L+ 3.5 c.c. The toxin had been reduced in toxicity by the action of formaldehyd

7. Zingher, A., and Park, W. H.: Immunity Results Obtained in School Children with Diphtheria Toxoid (Modified Toxin), Proc. Soc. Exper. Biol. & Med. **21**:383 (April) 1924.

and exposure to incubator temperature to the extent that 150 times the original amount of toxin represented one minimum lethal dosage. The combining power of the toxoid for antitoxin, however, had diminished much less, about ten times the amount of the original L+ being represented by the new L+. The toxoid was diluted with salt solution, 1:20, 1:14 and 1:10, representing 5, 7.5 and 10 per cent. of the preparation.

The amino-acid nitrogen content of this toxoid, as determined by the van Slyke method, was 4.5 mg. for each 10 c.c.

(*b*) Toxoid 377 was prepared from another toxin, which had a minimum lethal dosage of 0.01 c.c. and an L+ of 0.27 c.c. One liter of the formaldehyd treated toxin, which had been kept in the incubator for four weeks and one liter which had been kept for five weeks, were mixed together and standardized. The new minimum lethal dose was approximately 1.0 c.c. (1.0 c.c. killed a guinea-pig in 4.5 days) and the L+ was 5.0 c.c. In contrast with Toxoid 437 this preparation had not lost as much in toxicity, yet in combining power as represented by the L+ dose it was only about one-half as strong. The amino-acid nitrogen content of this toxoid was 5.1 mg. per 10 c.c. These differences probably explain the difference in immunizing value noted between the two preparations.

(*b*) LOCAL AND CONSTITUTIONAL REACTIONS AFTER INJECTIONS OF TOXOID

The reactions following the injections of toxoid were rather mild when compared with those noted after injections of the old type 3 to 5 L+ mixtures of toxin-antitoxin. The protein effect of the diluted toxoid was slightly more marked than that of the 0.1 L+ mixtures of toxin-antitoxin. This was due to the dilution of the toxoid being from ten fold to twenty fold as compared with the thirty fold dilution of the toxin in the 0.1 L+ toxin-antitoxin. The local toxic effect, however, of the diluted toxoid was decidedly less pronounced than after the 0.1 L+ mixtures. This was due to the fact that each dose of toxoid represented only from one-twentieth to one-thirtieth of a minimum lethal dosage, as compared with the one-eighth minimum lethal dosage in each dose of the toxin-antitoxin.

(*c*) IMMUNITY RESULTS WITH TOXOID

Table 8 shows the results noted with Toxoid 437. It was diluted to 5 per cent. (1:20) for Group A, to 7.5 per cent. (1:14) for Group B and to 10 per cent. (1:10) for Group C. The table shows the results with two doses and with three doses of 1 c.c. each, given at intervals of from one to two weeks. Over 1,800 injected children were retested.

Groups A and B have been added together. With two doses of the toxoid, sixty-one of eighty-three children, or 75.2 per cent., became immune; with three doses, 378 of 401 children, or 94.2 per cent., were successfully immunized. In Group C the toxoid, although less diluted, gave somewhat poorer results. Of 245 children receiving two doses, 167 or 68.1 per cent., became immune and gave a negative Schick retest; of 1,012 children receiving three doses 870, or 86.0 per cent., were immunized and showed a negative reaction at the retest.

TABLE 8.—*Results of Active Immunization with Diphtheria Toxoid (Modified Toxin) (Zingher)*

Preparation No. 437. Tests by Banzhaf
Minimum lethal dosage of toxin two years ago, 0.001 c.c.
Before modification with 0.1 per cent. formaldehyd, minimum lethal dosage 0.01 c.c. L + 0.32 c.c.
After modification with 0.1 per cent. formaldehyd and after five weeks in thermostat, minimum lethal dosage 1.5 c.c. (150×) (Weaker). L + 3.5 c.c. (10×) (Weaker)
Nitrogen content by van Slyke method, 4.5 mg. per 10 c.c.

		Original Schick Test		Diluted Toxoid 1 C.c.				Two Doses Toxoid			Three Doses Toxoid		
	Public School	Number Tested	Per Cent. Positive	Dilution	Per Cent. in Dilution	Mos. after Injection	Total Retested	Number	Schick Negative	Per Cent. Negative	Number	Schick Negative	Per Cent. Negative
A.	103 M.*.....	471	37.1	1:20	5.0	3	136	24	12	50.0	112	94	84.0
B.	14 M.	686	18.5	1:14	7.5	3	125	25	20	80.0	100	98	98.0
	19 M.	841	22.0	1:14	7.5	3	142	20	15	75.0	122	120	98.3
	83 M.	625	17.3	1:14	7.5	3	81	14	14	100.0	67	66	98.5
	Total.....	2,152	....	....	....	..	484	83	61	75.2	401	378	94.2
C.	15 M.	714	25.6	1:10	10.0	3	145	11	20	55 0	134	141	95.0
	23 Bx.*.....	600	24.8	1:10	10.0	3	98	15	11	73.3	83	77	92.7
	11 Bx.	205	69.2	1:10	10.0	3	118	51	35	68.6	67	62	92.5
	32 Bx.	174	30.0	1:10	10.0	3	29	3	2	66.6	26	24	92.3
	20 M.	713	15.0	1:10	10.0	3	106	20	12	60.0	86	79	91.8
	3 Bx.	741	24.4	1:10	10.0	3	132	27	21	77.7	105	94	90.4
	68 M.	642	49.5	1:10	10.0	3	210	48	24	50.0	162	133	83.0
	85 M.	725	11.1	1:10	10.0	3	43	16	12	75.0	27	24	81.5
	54 M.	349	51.7	1:10	10.0	3	102	21	12	57.1	81	60	74.0
	61 M.	1,253	25.5	1:10	10.0	3	274	33	18	54.5	241	176	73.0
	Total.....	6,116	....	....	....	..	1,257	245	167	68 1	1,012	870	86.0

* M., Manhattan; Bx, Bronx.

The results with this preparation of toxoid compare quite favorably with the immunity results formerly noted with many mixtures of toxin-antitoxin. As shown by Zingher [8] in judging the immunizing value of a preparation of toxin-antitoxin, it is necessary to consider other factors besides the mixture itself. One of the most important of these is the previous exposure and slight immunization by contact of the injected children. It was found that the children of the poorer classes,

8. Zingher, A.: Results of Active Immunization with Diphtheria Toxin-Antitoxin in the Public Schools of New York City, J. A. M. A. **78**:1945-1951 (June 24) 1922.

showing a low percentage of positive reactions at the original test, when injected with the same preparation of toxin-antitoxin, gave a better antitoxin response than those of the more well-to-do, who had been kept fairly segregated and had had only slight exposure to repeated contact infection with the diphtheria bacillus. To a certain extent the same factors were found to hold true in the immunity results noted after injections of toxoid.

Table 9 gives the results with Toxoid 377. The immunity response was much poorer than with Toxoid 437. The dilution of the toxoid used in these schools was 5 per cent. (1:20). In other schools we injected the toxoid in a dilution of 7.5 per cent. (1:14), and these

TABLE 9.—*Results of Active Immunization with Diphtheria Toxoid (Modified Toxin) (Zingher)*

Preparation No. 377
Minimum lethal dosage of toxin two years ago, 0.001 c.c
Before modification with 0.1 per cent. formaldehyd, minimum lethal dosage 0.01 c.c. L + 0.27 c.c.
After modification with 0.1 per cent. formaldehyd after five weeks in thermostat, minimum lethal dosage 1.00 c.c. (100 ×) (weaker). L + 5.0 c.c. (18.5 ×) (weaker)
Nitrogen content by van Slyke method, 5.1 mg. per 10 c.c.

	Original Schick Test					Two Doses Toxoid			Three Doses Toxoid		
Public School	Number Tested	Per Cent. Positive	Toxoid Dilution	Mos. after Injection	Total Retested	Number	Schick Negative	Per Cent. Negative	Number	Schick Negative	Per Cent. Negative
105 Manhattan.....	296	32.0	1:20	3	71	00	00	00.0	71	36	50.7
51 Manhattan.....	399	21.0	1:20	3	88	13	10	76.9	75	44	58.6
84 Manhattan.....	330	31.2	1:20	3	61	19	6	31.5	42	21	50.0
37 Bronx.....	357	26.3	1:20	3	61	4	2	50.0	57	16	27.4
Total.....	1,382	....	....	..	281	36	18	50.0	245	114	46.5

schools will be retested within a few months. With three doses of the 1:20 toxoid dilution, only 114 out of 245, or 46.5 per cent., were successfully immunized. The explanation given, that the actual combining value of this toxoid preparation was less than that of Toxoid 437, even though its toxicity for the guinea-pig was greater, probably explains these results.

The retests in the schools shown in Tables 6 and 7 were given from 2.5 to 3 months after the injections. Zingher has found in his work with toxin-antitoxin that a second Schick test made a year later on the positive reactors will show that more than 50 per cent. will have become immune without their having received further injections of toxin-antitoxin. It is interesting to note in this connection that many of the children who are shown in Tables 8 and 9 as persistent positive Schick reactors, gave a much weaker reaction than in the original test. It is probable, therefore, that many will show a negative Schick reaction at a later retest.

COMMENT

The value of toxoid as an immunizing agent against diphtheria lies in its easy and simple preparation and standardization. It is also a very safe preparation to use.

The possibility that persons become sensitized to horse serum by the injections of toxin-antitoxin was indicated by the intradermal tests reported by Hooker.[9] A repetition of Hooker's investigations by one of us [10] gave somewhat different results, in that while those injected with toxin-antitoxin showed on retest an increased percentage of skin reactions to horse serum, yet this was much less than Hooker found. There is also great doubt as to the importance of the slight amount of sensitization. The knowledge of an immunization should not cause us to withhold antitoxin as persons have been repeatedly injected with antitoxin after previous injections of toxin-antitoxin, and no greater amount of clinical symptoms of sensitization was noted than after injections in persons who had not previously received toxin-antitoxin. However, to obviate even the slight possibility of danger, goat antitoxin is being substituted now for horse antitoxin in the preparation of toxin-antitoxin.

An observation made by Zingher [7] in connection with the Schick retests after immunization with one-tenth L+ mixtures of toxin-antitoxin is significant in connection with the question of sensitization after injections of these mixtures. He found that not only were from 80 to 95 per cent. of the injected children immunized, but also that over 50 per cent. of these children showed slight to marked pseudoreactions in the Schick retest. With the 3 to 5 L+ mixtures such a high percentage of pseudoreactions was never noted at the retests. The question comes up whether very small amounts of proteins contained in the one-tenth L+ mixtures are not apt to be sensitized to a somewhat more intense degree than the larger amounts represented by the 3 to 5 L+ mixture. Whatever the explanation may be, this sensitization after one-tenth L+ mixtures has no clinical significance except so far as indicating the necessity for the sake of accuracy for always making a control test when the Schick retest is made to check up on the immunity results.

More important than the question of sensitization to horse serum after toxin-antitoxin injections, is the recent experience of White [11]

9. Hooker, S. B.: Human Hypersensitiveness Induced by Very Small Amounts of Horse Serum, J. Immunol. **9**:7-16 (Jan.) 1924.

10. Park, W. H.: Human Hypersensitiveness to Whole Horse Serum or Serum Globulins Following Diphtheria Toxin-Antitoxin Injections—Its Importance, J. Immunol. **9**:17-24 (Jan.) 1924.

11. White, B., and Robinson, E.: Effect of Exposure to Low Temperatures on Diphtheria Toxin-Antitoxin Mixture, J. A. M. A. **82**:1675 (May 24) 1924.

that a preparation of 1 L + of toxin-antitoxin after freezing became toxic, which has added further interest to the possibility of substitution of toxoid for toxin-antitoxin. Even though further investigation showed that the 0.1 L + preparation never became more toxic,[12] yet a certain opposition, unreasonable though it may be, has developed among a portion of the lay population against the use of toxin-antitoxin which will be eliminated by the substitution of toxoid.

Further work no doubt remains to be done in perfecting toxoid as an immunizing agent against diphtheria. Similar work had to be carried out with toxin-antitoxin. But the results noted in this communication are sufficiently encouraging to continue the work on an increasing scale and to aim for a more perfect preparation. There is no immediate urgency to substitute toxin-antitoxin by toxoid. If, however, as is probable, a toxoid can be elaborated that will serve as a good immunizing agent, the time will not be far distant when such substitution will be found of advantage.

CONCLUSIONS

1. Both the new toxin-antitoxin and the toxoid preparations give good immunizing results with but slight local and constitutional reactions.

2. The toxoid has advantages in that there is no horse serum in it to cause sensitization, which happens to a slight degree with toxin-antitoxin. The substitution of goat antitoxin for horse antitoxin will obviate this difficulty and this change is now being made.

3. Such a toxoid would do away with the fear in the population created by the recent experience with frozen toxin-antitoxin.

4. A satisfactory toxoid preparation is probably easier to make and also more stable.

5. In making toxoid by the addition of formaldehyd to toxin, care has to be taken of the amount of formaldehyd added and the period of time the formaldehyd treated toxin is exposed to the temperature of the incubator. The amount of amino-acid nitrogen, as determined by the van Slyke method, has a definite bearing on the amount of formaldehyd that is necessary to be added. Many of the toxin preparations containing from 2.5 to 5 mg. of nitrogen per 10 c.c. will require the addition of 0.1 per cent. formaldehyd and the exposure in the incubator from four to five weeks.

6. Careful tests of the minimum lethal dosage, the L + and the flocculating value of the toxoid should be made in standardizing the preparation. The minimum lethal dosage represents the remaining trace of free acting toxin, the L + and the flocculating value, the combining

12. Letters in J. A. M. A. **82**:567 (Feb. 16) 1924, by E. R. Kelly, G. W. McCoy, M. J. Rosenau and Wm. H. Park.

power of the toxoid. The combining value of toxoid serves as a good index of its immunizing value. It is of advantage to have a slight excess of free toxin (from $\frac{1}{15}$ to $\frac{1}{20}$ minimum lethal dosage in each dose) in the toxoid.

7. Toxoid and toxin-antitoxin should be carefully studied and, if possible, improved, and the one that is shown to be the best adopted for general use.

ABSTRACT OF DISCUSSION

DR. FRANK C. NEFF, Kansas City, Mo.: This work is unique in the studies made and in the preparation of the toxin mixtures. An unprecedented number of children have been immunized in New York. If the addition of liquor formaldehyd and the aging of the toxin will increase the unit antigenic power of the mixture, it will cause a marked improvement and refinement in the method. This progress is going on steadily from year to year. Any refinement of technic that will shorten the period of development of active immunity, decrease toxic reactions, and increase the percentage of successful immunization, will be of great benefit. These are the chief problems in carrying out active immunization. One cannot tell parents how long it will take to develop immunization, or even if it will always develop. Therefore, any improvement in the time factor is of great value. Dr. Zingher did not say whether with the toxoid preparation immunity takes place in a shorter time than with the one-tenth L + dose.

DR. C. A. EARL, Des Plaines, Ill.: Behring is dead. He was the first one to use the toxin-antitoxin mixtures, and it looks as if Theobald Smith, Park and Zingher will also be dead before these measures receive the attention they deserve. Two years ago I read a paper on this subject, in which I asked why we should not let the public health officers do the testing and then the children could be sent to the family doctor for the toxin-antitoxin injections. One prominent medical man said that it was not fair to the physician to let the state do any of the work, that the physicians should do the testing. The next year I met him and asked him if he had done any testing and he had to confess that he had not made a single test. I am surprised that these preventive measures are not more generally used. There seems to be an unwarranted mystery surrounding the Schick test and its interpretation. It is not absolutely necessary to inject the toxin into the skin. If given subcutaneously you can get good results. A year ago we had a diphtheria epidemic. I took pains to test and retest all the children exposed to diphtheria. Of 734 children who had given a negative Schick test, only one developed a possible case. Of thirty-four positives, seventeen developed clinical diphtheria.

DR. ABRAHAM ZINGHER, New York: I wish to emphasize the difference we noted in the immunity results with the two preparations of toxoid. The first preparation, although less toxic than the second, had a greater amount of toxoid. This was evidenced by the smaller L+ dose. We are studying at the present time the flocculation test of Ramon to determine the total combining elements in each of these two toxoid preparations. The immunity results were significant. With the first toxoid, diluted from ten to twenty times, from 86 to 94 per cent. of the injected children gave a negative Schick retest. With the second toxoid, we have retested so far only the schools in which a dilution of 1:20 of the toxoid had been used. Of the retested children we found that only 46.5 per cent. gave a negative Schick reaction. In answer to Dr. Neff's question I might say that the development of antitoxin after toxoid injections is just about as slow as after toxin-antitoxin injections. The Schick retest should not be made before three, or preferably six months.

THE USE OF THEOBROMIN SODIO SALICYLATE (DIURETIN) IN THE TREATMENT OF HYDROCEPHALUS *

W. McKIM MARRIOTT, M.D.

ST. LOUIS

Hydrocephalus results when there is an excessive secretion of spinal fluid, or diminished absorption.[1] A number of ingenious surgical procedures have been devised for the relief of hydrocephalus, and at times brilliant results have been obtained. The operative mortality, however, is extremely high. Repeated lumbar or ventricular puncture is generally used as a means of controlling the rapidity of development of hydrocephalus. Medical means of controlling the secretion or absorption of the cerebrospinal fluid have, up to the present time, met with indifferent success. There is some evidence that the administration of thyroid by mouth diminishes the secretion of cerebrospinal fluid.[2] In general, however, thyroid therapy in hydrocephalus has been disappointing.

In the course of some observations on edema,[3] it was found that when the surface tension of the blood was low, fluids tended to pass out of the blood and into serous cavities and intercellular spaces, and that when the surface tension of the blood was again raised fluid tended to pass in the opposite direction. It was found, furthermore, that certain of the purin diuretics, notably theobromin sodio salicylate (diuretin), when given by mouth, lead to a distinct raising of the blood surface tension. Reasoning from these findings, one might expect that lowering of the surface tension of the spinal fluid or raising of the surface tension of the blood would result in passage of fluid from the subarachnoid spaces into the blood, or in other words, increased absorption of spinal fluid.

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* Received for publication, Aug. 6, 1924.

* From the Department of Pediatrics, Washington University School of Medicine, and the St. Louis Children's Hospital.

* Read before the American Pediatric Society, Pittsfield, Mass., May 27, 1924.

1. Dandy, W. E., and Blackfan, K. D.: Internal Hydrocephalus, Am. J. Dis. Child. **8**:406 (Dec.) 1914. Frazier, C. H., and Peet, M. M.: Factors of Influence in the Origin and Circulation of the Cerebrospinal Fluid, Am. J. Physiol. **25**:3, 1914.

2. Frazier, C. H.: Types of Hydrocephalus—Their Differentiation and Treatment, Am. J. Dis. Child. **11**:95 (Feb.) 1916.

3. Marriott, W. McKim, and Clausen, S. W.: Intoxications Associated with Alterations in the Physico-Chemical Equilibria of the Body Cells and Fluids: I. Acute Bright's Disease, Proc. Am. Ped. Soc. **35**:205, 1923.

Acting on this hypothesis, we have administered diuretin to infants with hydrocephalus, and have obtained excellent results in a small series of cases of the communicating type. No beneficial effect was observed in cases where there was complete obstruction of the ventricles. We have, to date, been able to observe the effect of treatment in six patients. One of these has been under observation for almost a year. We feel that we have been able to rule out the element of coincidence and to demonstrate a definite effect of the diuretin. We have found, furthermore, that if the hydrocephalus can be controlled for a time, there is a possibility of ultimate spontaneous improvement.

These points are very well brought out in the following cases.

REPORT OF CASES

CASE 1.—R. F., a girl, aged 5 months, who entered the St. Louis Children's Hospital had been normal up to the age of 3 months, at which time she developed definite meningeal symptoms with fever. Following this attack the head had increased rapidly in size. There was marked hydrocephalus, the fontanels were bulging and the sutures were wide open. The maximum circumference of the head was 44.5 cm. (normal 41.5). The child was undernourished and there was a general hypertonicity. Lumbar puncture showed clear fluid under marked pressure. Pressure on the fontanel caused fluid to spurt from the lumbar puncture needle. The Wassermann reaction was negative on blood and spinal fluid.

The child remained under observation for one month, and during this time two lumbar punctures were done and from 50 to 75 c.c. of fluid removed. Each puncture caused a temporary decrease in the size of the head, but subsequent to the puncture the head continued to increase at a rapid rate. The child was taken home and was not seen again until two and one-half months later, when she returned to the clinic. The circumference of the head had increased to 51 cm. and the child was in bad condition. Lumbar puncture was performed and a large amount of fluid removed. This decreased the size of the head 0.75 cm. but increase occurred during the following days.

Diuretin was then begun in a dosage of 0.2 gm. three times daily, by mouth. This was continued for a period of six weeks. At the end of this period the head was exactly the same size as at the beginning.

In order to determine whether or not the diuretin was responsible for the stationary size of the head, treatment was interrupted for two weeks, and during this interval the head again increased in size at the former rate, and the fontanels became distinctly more tense. Diuretin was again administered and this was kept up for three and one-half months, during which time there was absolutely no increase in the size of the head. Treatment was again interrupted and during the next two and one-half months there was only a small increase in size.

In Chart 1 the results of treatment are given in graphic form. The line plotted out represents the maximum circumference of the head. This chart shows very well the failure of lumbar puncture to effect more than transient improvement. The chart illustrates the definite influence of diuretin, and further shows that after a prolonged period of treatment spontaneous improvement is possible. The head is not now increasing nearly so rapidly as originally. From the results, it would seem probable that a small dose of diuretin from now on should be capable of controlling the hydrocephalus, and it is not unlikely that treatment can ultimately be discontinued.

It should be mentioned that this child gained weight at a normal rate during the entire period of treatment. There were no untoward results that could be attributed to the medication employed. It was noted, however, that during

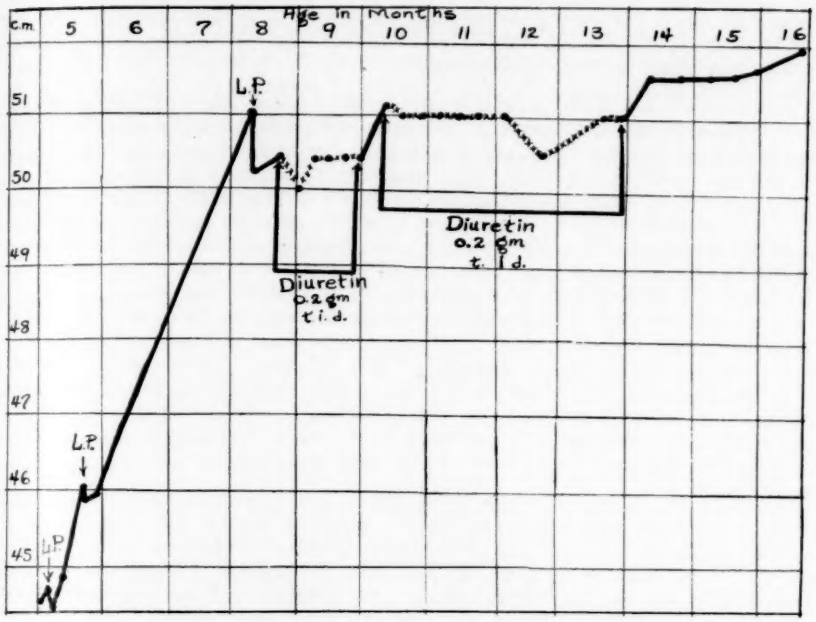

Chart 1 (Case 1, R. F.).—Illustrating maximum circumference of head; solid black line, growth of head without medication; dotted line, growth of head with diuretin medication.

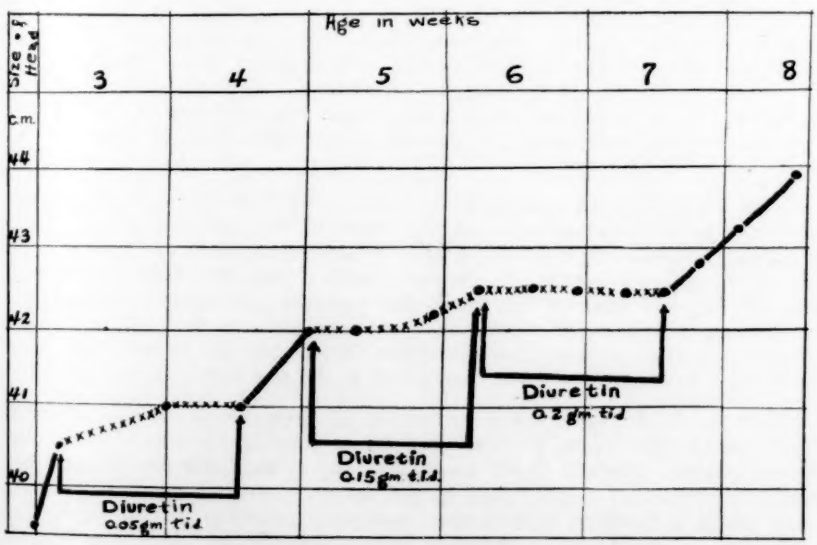

Chart 2 (Case 2, C. L.).—Illustrating maximum circumference of head; solid black line, growth of head without medication; dotted line, growth of head with diuretin medication.

the periods of diuretin treatment the skin and subcutaneous tissue became unusually firm and hard, resembling sclerema. This was possibly due to removal of fluid from the intercellular spaces. The skin assumed its natural consistency when treatment was stopped.

CASE 2.—C. L. This patient is of interest because the hydrocephalus was of extremely rapid development. The infant was born with spina bifida. The meningeal sac was approximately 3 inches in diameter. The baby's head began to enlarge rapidly from birth. The child was brought to the hospital at the age of 3 weeks. The maximum circumference of the head at this time was 39.5 cm. (normal 35 cm.). During the next two days the circumference of the head had increased to 40.5 cm. (See Chart 2). Diuretin was then begun in a dosage of 0.05 gm. three times a day. This resulted in a decreased rate of enlargement of the head, but some enlargement occurred. The diuretin was discontinued and enlargement occurred at approximately twice the rate as previously. Diuretin was then begun in larger doses (0.15 gm. three times a day) and during the next ten days there was an increase of only 0.5 cm. The dosage of diuretin was then increased to 0.2 gm. three times a day, with the result that the head remained at constant size for the next eight days. Treatment was again discontinued and during the next five days there was an increase of approximately 1.5 cm. The effect of the diuretin in this case was definite.

CASE 3.—W. O., a boy, aged 12 months. The immediate affect of diuretin therapy is shown very well in this child, who was normal until the age of 6 months, when he had a febrile disturbance. Following this the head enlarged rapidly. The legs also became spastic. At the age of 8 months, the head measured 48 cm.; at 12 months, 52 cm., an increase of 1 cm. a month. The spinal fluid was under increased pressure and there was communication between the ventricles and spinal subarachnoid. Diuretin in a dose of 0.2 gm. three times a day was given. At the end of two weeks the circumference of the head was 51.7 cm., a slight decrease.

CASE 4.—G. P., aged 7 months. A similar result was obtained in this child. This infant developed normally until the age of 4 months, when the mother noticed the head seemed to be enlarging at an abnormal rate. At the age of 7 months the head measured 48.5 cm. Sixty cubic centimeters of clear fluid was removed by lumbar puncture and the circumference of the head decreased to 45 cm. At the end of five days the circumference of the head had increased to 47 cm. Diuretin (0.2 gm. three times a day) was administered. No further lumbar punctures were done. At the end of two weeks the circumference had decreased to 44 cm.

CASE 5.—F. G., aged 2 months. In this case of complete obstruction of the ventricles no beneficial effect at all was observed from diuretin therapy. The head had increased rapidly and steadily in size since birth, and measured 46 cm. at the age of 2 months. On lumbar puncture very little fluid was obtained but 130 c.c. was removed by ventricular puncture. Diuretin was given and in addition a number of ventricular punctures were made. The head continued to enlarge, however, and the infant died at the end of two weeks. At necropsy a complete obstruction was found at the aqueduct.

CASE 6.—B. S., aged 1 day, in whom no favorable result was obtained. There was a spina bifida, and the head had enlarged at the rate of more than 1 cm. a week. Diuretin (0.065 gm. three times a day) did not influence the rate of increase. The child died at the age of 4 weeks. At necropsy there were found a number of congenital anomalies including a bilateral hydronephrosis. It could not be definitely determined whether there was definite obstruction to the flow of fluid from the ventricles. It is possible, in this case, that the hydronephrosis was a factor in preventing a favorable action of the diuretin.

COMMENT

From our experience with diuretin, we believe it to be a valuable remedy in the treatment of the communicating type of hydrocephalus. In the light of the extremely bad prognosis of patients with this condition, and the apparent harmlessness of the therapy, we feel that the method of treatment should be given a thorough trial before resorting to difficult and dangerous surgical procedures.

RÉSUMÉ OF THE LITERATURE ON SCARLET FEVER

THE HEMOLYTIC STREPTOCOCCUS AS THE CAUSE OF SCARLET FEVER *

GLADYS H. DICK, M.D.

EVANSTON, ILL.

EXPERIMENTAL SCARLET FEVER

Attempts to learn the cause of scarlet fever have long been hampered by failure to obtain the disease experimentally. Until 1923, experimental scarlet fever had not been produced in animals or in man by inoculation of a pure culture of any organism. Symptoms that might represent scarlet fever in animals had been described; but they were inconstant, and had followed inoculations with a variety of materials and cultures. No organism had produced, in animals, a clinical condition that could be accepted as experimental scarlet fever.

In January, 1923, Hektoen [1] published an interesting historical review of the attempts to produce experimental scarlet fever in man. The successful inoculation of smallpox, as a preventive measure, had led to the hope of a similar success from the inoculation of scarlet fever. Thus, as Erasmus Darwin, the grandfather of Charles Darwin, wrote:

"No one could do an act more beneficial to society, or glorious to himself, than by teaching humanity how to inoculate this fatal disease (scarlet fever); and thus deprive it of its malignanty. Matter might be taken from the ulcers in the throat, which would probably cause the contagion. Or warm water might be put on the eruption, and scraped off again by the edge of a lancet. These experiments could be attended with no danger, and should be tried for the public benefit, and the honor of medical science."

Most suggested that preventive inoculation should be practiced only in children between the ages of 2 and 7 years, not younger, because they are insusceptible, and not older, because they are too susceptible.

Attempts had been made to produce experimental scarlet fever in man by inoculation with material from erythematous areas; serum from miliary vesicles; skin scales; blood from scarlet fever patients; filtrates of throat mucus, and pure cultures of organisms isolated from scarlet fever.

Hektoen concluded that, up to January, 1923, there was on record no undoubted case of experimental scarlet fever in man. Accidental

* Received for publication, Aug. 12, 1924.

1. Hektoen, Ludvig: The History of Experimental Scarlet Fever in Man, J. A. M. A. **80**:84 (Jan. 13) 1923.

inoculations of human beings with materials of scarlet fever origin had been reported, but they had occurred under circumstances that threw no light on the etiology of the disease.

In connection with the negative results reported by Dick and Dick, in their first series of human experiments, Hektoen suggested that inoculations of volunteers from rural districts might be more successful.

Dick and Dick, after failure to obtain, with any degree of constancy, the clinical picture of scarlet fever in animals, had concluded that laboratory animals are comparatively insusceptible to the disease, and that the use of human volunteers would be necessary to the production of experimental scarlet fever. In 1921, they [2] reported their first series of human inoculations. In this series, they obtained an occasional sore throat and fever; but no case of experimental scarlet fever.

In their [3] next experiments, reported in the Autumn of 1923, they selected volunteers who came from rural districts, or from homes where an ordinary attack of scarlet fever would probably have been recognized. In this second series, they succeeded in producing two cases of experimental scarlet fever by inoculation with an apparently pure culture of a hemolytic streptococcus. This streptococcus was isolated from a lesion on the finger of a nurse who had contracted scarlet fever while caring for a convalescent scarlet fever patient. Five volunteers were inoculated by swabbing a culture of the streptococcus on the tonsils and pharynx. Three of these volunteers remained well. One had sore throat and fever, without a rash. The other developed scarlet fever. The incubation period, in this case, was about forty-eight hours. The disease was characterized by sore throat, general malaise, fever, nausea, leukocytosis, and a scarlatinal rash, followed by desquamation.

In order to learn whether or not this case of scarlet fever was caused by the hemolytic streptococcus, or by a filterable virus associated with it, another series of volunteers were inoculated with filtered cultures of the same organism. None of the volunteers inoculated with the filtrates developed scarlet fever. They were later inoculated with the unfiltered culture. Following inoculation with the unfiltered culture, two remained well; two developed sore throat and fever, but no rash, while the other volunteer had an attack of scarlet fever.

Dick and Dick concluded that the two cases of experimental scarlet fever described had been caused by the hemolytic streptococcus, and not by a filterable virus.

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2. Dick, Gladys F., and Dick, George H.: Experimental Inoculations in Scarlet Fever, J. A. M. A. **77**:782 (Sept. 3) 1921.

3. Dick, Gladys F., and Dick, George H.: Experimental Scarlet Fever, J. A. M. A. **81**:1166 (Oct. 6) 1923.

In their next article, Dick and Dick [4] state that the streptococci, associated with scarlet fever, may be divided into two groups according to their effect on mannite. The streptococcus concerned in their first cases of experimental scarlet fever fermented mannite. It was still important to know whether or not scarlet fever could be produced by a strain that did not ferment mannite. They isolated such an organism from the throat of a scarlet fever patient, and with it, produced another case of experimental scarlet fever. This was the last step necessary to fulfil all the requirements of Koch's laws, and they concluded that hemolytic streptococci, of the two cultural types used in their experiments, are the cause of scarlet fever.

These three cases of experimental scarlet fever in human beings were uncomplicated, and the volunteers made a complete recovery.

SCARLET FEVER TOXIN

The toxic element of scarlet fever has long been recognized by clinicians. Variation in the degree of toxemia has served as a basis for the differentiation of clinical types. Thus, Osler,[5] in describing the fulminant, toxic type of scarlet fever, wrote:

"With all the characteristics of an acute intoxication, the patient is overwhelmed by the intensity of the poison, and may die within twenty-four or thirty-six hours."

And Holt [6] said of the malignant type:

"Death occurs apparently from scarlatinal toxemia."

When the use of convalescent serum in the treatment of scarlet fever became more general, it was learned that it is the severe, toxic type of the disease in which it is the most useful; and that the symptoms most benefited by it are the symptoms commonly attributed to the toxemia.

In 1918, Schultz and Charlton [7] described the phenomenon now known as the Schultz-Charlton reaction. It consists of a local blanching of the scarlatinal rash about the site of an intracutaneous injection of convalescent scarlet fever serum. This test is sometimes used in the diagnosis of scarlet fever rashes.

In December, 1923, Mair [8] published his results with the Schultz-Charlton reaction, and concluded that this reaction is definite experi-

4. Dick, Gladys F., and Dick, George H.: The Etiology of Scarlet Fever, J. A. M. A. **82**:301 (Jan. 26) 1924.

5. Osler, William: Practice of Medicine, Ed. 6, New York, D. Appleton & Company, 1905, p. 134.

6. Holt, Luther E.: Diseases of Infancy and Childhood, Ed. 2, New York, D. Appleton & Company, 1904, p. 944.

7. Schultz and Charlton: Ztschr. f. Kinderh. **17**:328, 1918.

8. Mair, W.: An Immunity Reaction in Scarlet Fever, Lancet **2**:1390 (Dec. 29) 1923.

mental evidence of a toxin-antitoxin phenomenon in scarlet fever. He attributed the rash and other changes in the skin to the unknown scarlet fever toxin, and the blanching of the rash by convalescent serum to the neutralization of the toxin by an antitoxin in the serum of the convalescent patient.

After their first cases of experimental scarlet fever had been obtained by inoculation with a hemolytic streptococcus, and after the exclusion of a filterable virus as the cause of scarlet fever, Dick and Dick [9] sought to learn by what means the streptococcus, growing in the throat, produces the scarlatinal rash. They discovered that filtered cultures of the streptococcus contained a soluble toxin.

When suitable amounts of this toxin are injected in susceptible persons, it may cause general malaise, nausea, vomiting, fever, and a generalized scarlatinal rash. In other words, the sterile toxin, alone, is capable of producing the characteristic symptoms of scarlet fever, including the rash.

They found that the toxin is neutralized by incubation with convalescent serum, due to the presence of an antitoxin in the blood of recovered patients. If persons susceptible to scarlet fever are immunized by injections of small doses of the toxin, their blood serum acquires similar antitoxic properties.

They concluded that they were dealing with a true soluble toxin, specific for scarlet fever.

This toxin is resistant to heat at temperatures ordinarily employed to kill bacteria.

While small quantities of this toxin will produce symptoms of scarlet fever in susceptible human beings, laboratory animals are comparatively insusceptible to it; so that it is necessary to standardize the toxin on human beings.

SKIN TEST FOR SUSCEPTIBILITY TO SCARLET FEVER

After demonstration of the specific toxin, Dick and Dick [10] found that weak solutions of the toxin may be employed in skin tests to determine susceptibility to scarlet fever. The toxin is first carefully standardized, and diluted so that 0.1 c.c. represents a skin test dose. The test consists of an intradermal injection of exactly 0.1 c.c. of the skin test dilution on the flexor surface of the forearm. The reaction is observed at the end of twenty-four hours. An area of reddening, 1 cm. in diameter, represents some degree of susceptibility to scarlet fever.

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9. Dick, Gladys F., and Dick, George H.: Scarlet Fever Toxin in Preventive Immunization J. A. M. A. **82**:544 (Feb. 16) 1924.

10. Dick, Gladys F., and Dick, George H.: A Skin Test for Susceptibility to Scarlet Fever, J. A. M. A. **82**:265 (Jan. 26) 1924.

In a series of skin tests, reported in January, 1923, Dick and Dick found positive, or strongly positive, reactions in 41.6 per cent. of the persons who gave no history of scarlet fever; and negative, or only slightly positive reactions, in all of the convalescent scarlet fever patients tested.

This skin test was developed before they attempted to produce experimental scarlet fever with the type of streptococcus that does not ferment mannite. In selecting their volunteers for inoculation with this type of streptococcus, they chose one with a negative skin reaction, and one with a positive reaction. Both volunteers were inoculated with the same culture. The one with a negative skin test remained well; while the volunteer who had shown a positive test developed scarlet fever.

In the instances where they had an opportunity to observe the skin reaction before and after an attack of scarlet fever, it was positive before the attack, and negative during convalescence.

These authors also found that if persons, with positive skin tests, received convalescent scarlet fever serum intramuscularly, their skin tests became negative.

They concluded that the skin test with scarlet fever toxin bears a specific relation to susceptibility to scarlet fever.

Branch and Edwards [11] made skin tests, using the Dick toxin, and a control of heated toxin. In their series, they found negative skin reactions in all of the convalescent scarlet fever patients tested. Three patients, acutely ill with scarlet fever, gave slightly positive reactions, which became negative during convalescence. They obtained 40 per cent. positive, or strongly positive, reactions with the same filtrate that the Dicks used. All of the tests made with heated toxin were negative.

Branch and Edwards concluded that the skin test, with the filtrate of the Dicks, apparently has a specific relationship to immunity to scarlet fever.

Zingher [12] found a similar relation between immunity to scarlet fever and skin reactions to scarlet fever toxin. He found that some persons show positive reactions with heated toxin, and described this as a pseudoreaction.

Zingher showed that there is a parallelism between immunity to scarlet fever and immunity to diphtheria. Most infants show negative reactions during the first months of life, and the skin test becomes

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11. Branch, C. F., and Edwards, F. G.: The Relation of the Dick Test to Scarlet Fever, J. A. M. A. **82**:1260 (April 19) 1924.

12. Zingher, A.: Further Studies with the Dick Test and Active Immunization with Scarlet Fever Streptococcus Toxin, Proc. Soc. Exper. Biol. & Med. **21**:508 (May) 1924.

positive toward the end of the first year. These results are in striking agreement with the conclusion as to the insusceptibility of young children that Most expressed nearly one hundred years ago.

PREVENTIVE IMMUNIZATION TO SCARLET FEVER

Active Immunization.—As related by Hektoen, in his survey of the attempts to produce experimental scarlet fever in man, many attempts have been made to inoculate human beings with scarlet fever in the hope of preventing more severe attacks.

The most extensive use of vaccines, for the prevention of scarlet fever, was in Russia. This procedure was introduced by Gabritschewsky [13] in 1905. The vaccine was prepared from broth cultures of strains of hemolytic streptococci isolated from scarlet fever. These cultures were heated at 60 degrees, and preserved with 0.5 per cent. phenol (carbolic acid). Three subcutaneous injections of the vaccine were given. Altogether, the vaccine was employed in about 50,000 cases. Mild attacks of scarlet fever, with rashes, either local or generalized, were described, following administration of the vaccine.

In the light of our present knowledge of scarlet fever toxin, it seems probable that this toxin was present in the broth cultures used in the preparation of Gabritschewsky's vaccine, and that the toxin was not completely destroyed or removed in the preparation of the vaccine. So that, while they believed their results to be due to a streptococcus vaccine, the rashes and any degree of immunity obtained, might well have been due to toxin, unwittingly injected along with the killed streptococci.

Dick and Dick [14] attempted to immunize susceptible persons by injections of small amounts of scarlet fever toxin. They found that, by proper dosage, they were able to immunize persons with positive skin tests so that their skin tests became negative, and they did not contract scarlet fever on exposure.

They report a series of 125 persons exposed to scarlet fever. In this series, sixty-three showed negative skin reactions, and were not immunized. Fifty-two had positive skin tests, and were immunized with toxin. None of these persons contracted scarlet fever. They emphasize the importance of carrying the immunization to the point of a negative skin test. By employment of three doses of toxin, they have been able to eliminate severe reactions.

Passive Immunity.—Since the employment of convalescent scarlet fever serum in acute scarlet fever this serum has been used to some

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13. Gabritschewsky: Centrlb. f. Bakteriol **41**:719 and 844, 1906; Berl. klin. Wchnschr. **44**:556, 1907.

14. Dick, Gladys F., and Dick, George H.: The Prevention of Scarlet Fever, J. A. M. A. **83**:84 (July 12) 1924.

extent as a prophylactic treatment. The results with it have been inconstant. Dick and Dick [10] found that injection of convalescent serum would bring about a negative skin test in a person who had previously shown a positive reaction. But in the case they report (that of a nurse with a strongly positive skin test) a total amount of 30 c.c. of convalescent serum was required to produce a negative skin test. This is a larger quantity than has usually been given in prophylactic treatment. It may be that failure of convalescent serum to protect in some cases has been due to the insufficient quantity administered.

Dick and Dick [14] employ passive immunization with convalescent serum after exposure to scarlet fever, if the skin test is positive, and throat cultures on blood agar plates show colonies of hemolytic streptococci. In ten such cases, treated with convalescent serum, after exposure, no case of scarlet fever developed.

As controls, they offered a series of thirty-two nurses and interns on whom skin tests were not made, and two nurses, with positive skin tests, who were exposed to scarlet fever before their immunization was completed. These two nurses and five others of this control series contracted scarlet fever.

ANTISTREPTOCOCCIC SERUM IN SCARLET FEVER

In 1895, Marmorek obtained an antistreptococcic serum by immunizing horses with living streptococci. This serum was not produced with a view to its use in scarlet fever alone, but with the idea that it would be helpful in all streptococcus infections.

Since then, many antistreptococcic serums have been prepared for use in scarlet fever. Of these serums, the one most widely used was that described by Moser, in 1902. Moser immunized horses with living cultures of streptococci, cultivated from the heart's blood of fatal cases of scarlet fever. He reported, in detail, a series of cases treated with his serum, and two control series; one with Marmorek's serum, and one with normal horse serum. There can be little doubt that Moser's serum exerted a favorable influence on the rash, temperature, and general condition in many cases of scarlet fever. But it was necessary to give it in large doses: from 30 to 100 and even 200 c.c. Its use was gradually abandoned, on account of the severe serum reactions to which some deaths had been attributed.

In 1924, Dochez and Sherman [15] described an antistreptococcic serum for use in scarlet fever. This serum was also obtained by immunizing horses with living cultures of hemolytic streptococci isolated from

15. Dochez, A. R., and Sherman, Lillian: The Significance of Streptococcus Hemolyticus in Scarlet Fever, J. A. M. A. **82**:542 (Feb. 16) 1924.

scarlet fever. The method of immunization differed in detail from that employed by Moser in that, while Moser injected serum broth cultures of the streptococci, Dochez and Sherman injected agar cultures.

They demonstrated that the serum obtained in this way is capable of producing the Schultz-Charlton reaction in scarlet fever; thus furnishing evidence that the serum contains an antitoxin capable of neutralizing the scarlet fever toxin.

Although Dochez and Sherman concurred in the toxin-antitoxin theory of scarlet fever, and attributed the action of their serum to the presence of an antitoxin, they were unable to demonstrate the toxin described by Dick and Dick.

Blake, Trask, and Lynch [16] reported results with the antistreptococcic serum prepared by Dochez and Sherman in a series of thirteen cases of scarlet fever occurring in New Haven. They employed the serum in from 40 to approximately 200 c.c. amounts. They concluded that it possesses very marked curative properties. In their series, the one death results in a mortality of 7.6 per cent. Blake [17] later reported thirteen additional cases, bringing the mortality down to 3.8 per cent. in a series of twenty-six cases. These writers offered no control series. But the statistics of the New Haven Health Department show that, from the first of January to the first of April, 1924, out of 197 cases of scarlet fever in that city, there were only two deaths, resulting in a mortality of but 1 per cent. These figures indicate that a larger series of cases, with adequate controls, is desirable.

In his second report, Blake [17] states that all of the patients treated with the antistreptococcic serum developed serum disease.

SCARLET FEVER ANTITOXIN

Dick and Dick [18] immunized horses by subcutaneous injections of sterile scarlet fever toxin, and obtained an antitoxin of such strength that 10 c.c. neutralized twenty times the amount of toxin which caused nausea, vomiting, fever, and a scarlatinal rash in susceptible adults. They then concentrated this serum by the method commonly employed for concentration of other antitoxic serums. They state that the resulting product is of higher antitoxin content, and should cause fewer serum reactions than the unconcentrated serum.

They suggest that this concentrated scarlet fever antitoxin may be employed in passive immunization when convalescent serum is not

16. Blake, F. G.; Trask, J. D., and Lynch, J. F.: Observations on the Treatment of Scarlet Fever with Scarlatinal Antistreptococcic Serum, J. A. M. A. **82**:712 (March 1) 1924.

17. Blake, F. G.: Treatment of Scarlet Fever with Scarlatinal Antistreptococcus Serum, Abstr., J. A. M. A. **82**:1721 (May 24) 1924.

18. Dick, Gladys F., and Dick, George H.: A Scarlet Fever Antitoxin, J. A. M. A. **82**:1246 (April 19) 1924.

available. They are now using their antitoxin in the treatment of scarlet fever, but have made no claims as to its therapeutic value, saying that it will be necessary to wait until the results of its use in a large series of carefully controlled cases are available.

THE AGGLUTINATION OF STREPTOCOCCI IN SCARLET FEVER

Since the recognition of the specificity of the agglutination test, and its application to the diagnosis of typhoid fever, many observations have been made on the agglutination of streptococci in relation to scarlet fever. The results of the earlier investigators indicated that most, but not all, of the streptococci associated with scarlet fever are agglutinated by the same immune serum. The agglutination test had not furnished a means of differentiating streptococci of scarlet fever origin from those of other sources.

In 1920, Tunnicliff [19] concluded that the agglutination of streptococci is sufficiently specific to be of aid in the diagnosis of scarlet fever. Dochez and Bliss,[20] in the same year, concluded that the hemolytic streptococci found in the throats of scarlet fever patients may be readily distinguished from other streptococci by means of the agglutination test.

Dochez and Sherman [15] isolated streptococci from scarlet fever. From the organisms thus obtained they selected, by means of the agglutination test, strains for immunizing horses. They obtained in this way a specific serum, capable of blanching the scarlatinal rash on intradermal injection. They report no experiments to show that the streptococci, of scarlet fever origin, discarded because of their failure to agglutinate, were not capable of producing a similar serum.

More recently Dochez [21] has stated that the agglutination of streptococci isolated from scarlet fever patients is positive in only about from 75 to 80 per cent.

Dick and Dick [14] found no cross agglutination between the two strains of hemolytic streptococci with which they obtained experimental scarlet fever in human beings. While these two strains differ culturally in their effect on mannite, and are not agglutinated by the same immune serums, they have in common the property of producing the specific toxin of scarlet fever. They concluded that the agglutination test is not to be relied on for the identification of scarlet fever streptococci.

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19. Tunnicliff, Ruth: Specific Nature of the Hemolytic Streptococcus of Scarlet Fever, J. A. M. A. **74**:1386 (May 15) 1920.

20. Dochez, A. R., and Bliss, W. P.: Biologic Study of Hemolytic Streptococci from Throats of Patients Suffering from Scarlet Fever, J. A. M. A. **74**:1600 (June 5) 1920.

21. Stevens and Dochez: Proc. Soc. Exper. Biol. & Med. **21**:29, 1923; Dochez, A. R., Abstr., J. A. M. A. **82**:1641 (May 17) 1924.

Concerning the agglutination of streptococci by the blood serum of patients convalescent from scarlet fever, Bliss [22] concluded that the reaction is too limited to justify conclusions as to specificity.

Herrold and Tunnicliff [23] concentrated the blood serum of convalescent scarlet fever patients with ammonium sulphate. They describe a specific agglutination of scarlet fever streptococci by this concentrated serum.

THE WORK OF ITALIAN INVESTIGATORS

In 1921, G. DiCristina [24] described an anerobic diplococcus which he cultivated from scarlet fever. In 1923, Caronia and Sindoni [25] reported finding this diplococcus in cultures of the throat, blood, cerebrospinal fluid, and bone marrow of scarlet fever patients. They inoculated rabbits with cultures of the organism, and obtained a clinical picture which, in some respects, resembled scarlet fever. They found a specific agglutination, complement fixation, and opsonic index for this organism in scarlet fever.

They vaccinated one group of children with killed cultures of the diplococcus, and inoculated another group with living cultures. The children inoculated with living cultures developed a mild illness, which these investigators regarded as an attenuated form of scarlet fever. Neither the vaccinated children nor the inoculated children contracted scarlet fever on exposure.

Sindoni [26] later reported the cultivation of the same anerobic diplococcus from the rash and skin scales of scarlet fever.

Vitetti [27] cultivated the diplococcus from the throat secretions in scarlet fever, and confirmed the specific agglutination of the organism by the blood serum of convalescent scarlet fever patients.

Ritossa [28] found the organism in the urine during the course of scarlet fever; and Catteruccia [29] found it in the sediment, as well as in the cultures of the cerebrospinal fluid.

In March, 1924, Sindoni [30] reported that, of 291 persons who received vaccine prepared from the anerobic diplococcus, only one later developed scarlet fever.

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22. Bliss, W. P.: Bull. Johns Hopkins Hosp. **31**:173 (May) 1920; J. Exper. Med. **36**:575 (Nov.) 1922.
23. Herrold, R. D., and Tunnicliff, Ruth: Specific Streptococcus Agglutinins in Concentrated Scarlatinal Fever, J. Infect. Dis. **34**:209 (March) 1924.
24. DiCristina, G.: Pediatria **29**:1105 (Dec.) 1921.
25. Caronia, G., and Sindoni, M. B.: The Etiology of Scarlet Fever, Pediatria **31**:745 (July) 1923.
26. Sindoni, M. B.: Microorganisms of Scarlet Fever in the Eruption and in the Scales, Pediatria **31**:857 (Aug.) 1923.
27. Vitetti, G.: Etiology of Scarlet Fever, Pediatria **31**:989 (Sept.) 1923.
28. Ritossa, P.: The Etiology of Scarlet Fever, Pediatria **31**:992 (Sept.) 1923.
29. Catteruccia, C.: The Agent of Scarlet Fever, Pediatria **32**:31 (Jan.) 1924.
30. Sindoni, M. B.: The Vaccine Prevention of Scarlet Fever, Pediatria **32**:241 (March) 1924.

In May, 1924, Piatelli [31] reported the use of Caronia's vaccine in fifty-nine children during an epidemic of scarlet fever. None of these children contracted the disease.

In June, 1924, DeVilla [32] described a cutaneous test with cultures of this anerobic coccus.

SCARLET FEVER AS AN ANAPHYLACTIC PHENOMENON

In April, 1923, Meyer [33] published an article in which he ascribed the characteristic rash and eosinophilia of scarlet fever to an anaphylactic reaction, due to sensitization to the streptococcus protein.

Bristol,[34] in December, 1923, and Dabney,[35] in March, 1924, followed with articles in which they express the same opinion. Bristol attempted to demonstrate this hypersensitiveness by means of skin tests made with commercially prepared streptococci.

None of these authors offer any convincing experimental evidence in support of their theory.

THE WASSERMANN REACTION IN SCARLET FEVER

Since the report of Much and Eichelberg on the Wassermann reaction in scarlet fever, there has been a general impression that the test is commonly positive in this disease. This statement has even found its way into textbooks. Most of the positive reactions in scarlet fever were obtained by investigators who employed watery extracts of organs as antigens. Since then, many reports have been made on the Wassermann reaction in scarlet fever. Schleissner; Seligman and Klopstock; Halberstaedter, Müller, and Reiche; Gross and Folk; and Hoehne in 1908: Hecht, Lateiner, and Wilenko; Sommerfeld; and Fua and Koch in 1909: Noguchi in 1910: Kolmer in 1911: and Dick and Dick in 1916, reported negative results in scarlet fever with the use of alcoholic or acetone insoluble antigens. Most of these authors concluded that a positive Wassermann reaction in scarlet fever is an indication of syphilis.

In 1923, Christensen [36] reported Wassermann tests in 110 cases of scarlet fever. There were no positive reactions with the alcoholic

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31. Piatelli, A.: Preventive Vaccination in Scarlet Fever, Policlinico **31**:581 (May) 1924.

32. DeVilla: Intradermal Reaction in Scarlet Fever, Pediatria **32**:665 (June) 1924.

33. Meyer, S.: Scarlet Fever as an Anaphylactic Phenomenon, Deutsch. med. Wchnschr. **49**:509 (April) 1923.

34. Bristol, L. D.: Scarlet Fever as a Reaction of Hypersensitiveness to Streptococcus Protein, Am. J. M. Sc. **166**:853 (Dec.) 1923.

35. Dabney, Virginius: Is Scarlet Fever Merely a Streptococcic Anaphylaxis? J. A. M. A. **82**:956 (March 22) 1924.

36. Christensen, G. E.: The Wassermann Reaction in Scarlet Fever Patients, J. A. M. A. **80**:1118 (April 21) 1923.

antigen. Cholesterinized antigen gave ten transitory positive reactions. He concluded that scarlet fever does not interfere with the diagnostic value of the Wassermann reaction.

Dunlop [37] tested seventy-seven cases of scarlet fever without finding a positive reaction at any stage of the disease.

Potano,[38] in 1924, carried out Wassermann and Sachs-Georgi tests, using various antigens, in 135 cases of scarlet fever. In this series he found but four positive reactions, and these occurred in syphilitic patients. In the other cases, the tests were negative, except in some where an aqueous antigen was employed.

COMMENT

With such an accumulation of evidence, we are justified in attributing a positive Wassermann reaction, occurring during the course of scarlet fever, to syphilis, providing an alcoholic or an acetone insoluble antigen has been used in the test.

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37. Dunlop, E. M.: The Wassermann Reaction in Scarlet Fever, J. Path. & Bacteriol. **26**:196 (April) 1923.

38. Potano, P.: Reactions in Scarlet Fever, Policlinico **31**:219 (April) 1924.

Abstracts from Current Literature

Anatomy and Physiology

COLORIMETRIC DETERMINATION OF p_H IN PATHOLOGIC PLASMA BY CULLEN'S METHOD. JOHN MARRACK and F. C. SMITH, Brit. J. Exper. Pathol. **5**:13, 1924.

Estimations of carbon dioxid tension and carbon dioxid combining power were done in nineteen plasmas, some of which had abnormal total protein, globulin or fibrinogen contents, and the p_H was calculated by the formula of Austin, *et al.* These values did not differ by more than $\pm$ 0.03 from the values secured by the Cullen method, when the figure 0.23 was used to subtract from the apparent colorimetric p_H at 20 C. to convert to electrometric p_H at 37 C. Because of this fact they believe the figure 0.23 is correct for plasma and is very little influenced by varying amounts of protein in the plasma.

HOAG, New York.

Pathology and Bacteriology

BLOOD CHANGES AND CLINICAL SYMPTOMS FOLLOWING ORAL ADMINISTRATION OF PHOSPHATES. HARALD A. SALVESEN, A. BAIRD HASTINGS and J. F. MCINTOSH. J. Biol. Chem. **60**:311, 1924.

Sodium phosphate solutions given orally in large amounts over a short period of time to dogs produced tetany, irrespective of whether the acid or alkaline salt were given. Smaller quantities over a longer period caused no tetany. The tetany was due to a diminished calcium in the blood and was relieved by injections of calcium salt.

FAT EXCRETION. II. THE QUANTITATIVE RELATIONS OF THE FECAL LIPOIDS. WARREN M. SPERRY and W. R. BLOOR, J. Biol. Chem. **60**:261, 1924.

The authors have studied the kinds of lipoids present in the feces of cats and dogs under different conditions, viz., fasting, sham feeding (agar-agar and meat extract), diet high in olive oil (high iodin number) and diet high in cocoanut oil (low iodin number). The quantity of fat in the feces is not proportional to that in the diet. The type of fat in the feces tends to be much the same as that in the diet. The authors found that the blood and fecal lipoids were very similar in character and believe that the fatty material of the feces has its origin in the blood.

THE URIC ACID PROBLEM. AN EXPERIMENTAL STUDY ON ANIMALS AND MAN, INCLUDING GOUTY SUBJECTS. OTTO FOLIN, HILDING BERGLUND and CLIFFORD DERICK, J. Biol. Chem. **60**:361, 1924.

The authors have injected uric acid intravenously in various animals (dogs, cats, rabbits and goats) and also in normal men and in patients with gout. The accurate methods of analysis devised by Folin afforded the opportunity to study the uric acid contents of the blood and urine in these tests.

The experimental work seems to warrant the following conclusions. Uric acid is removed from the blood and body, either by destruction or by excretion through the urine. Destruction of uric acid occurs mostly in the blood and perhaps to some extent in the kidney. Uric acid is not destroyed by the blood in vitro. Uric acid tends to accumulate in the kidney tissue in high concentration following injection; this is later gradually returned to the blood stream

or excreted. There is practically no diffusion of the injected uric acid into the muscles or other organs. Different species of animals have varying capacity of destroying uric acid, herbiverous animals (rabbit, goat) destroying less uric acid than the dog. Human subjects vary greatly in their capacity to destroy injected uric acid. More of the injected uric acid is excreted if the subject is on a high protein diet. Patients with gout differ from the normal in that the blood contains a higher level of uric acid, because the kidneys do not accumulate uric acid normally, although excretion is of itself probably unimpaired. Gout does not interefere with the destruction of injected uric acid. Intravenous injections in most subjects result in malaise, but do not produce attacks of gout in patients with that disease. The injections in some cases cause a temporary impairment of the kidney function of excreting other nitrogenous substances.

THE EFFECT OF THE ADMINISTRATION OF CALCIUM SALTS ON THE INORGANIC COMPOSITION OF THE BLOOD. HARALD A. SALVESEN, A. BAIRD HASTINGS and J. F. MCINTOSH, J. Biol. Chem. **60**:327, 1924.

Experiments were made on the effects of administration of calcium chlorid and calcium lactate orally to dogs, and to two men with kidney lesions, and also of calcium chlorid intravenously to dogs. Calcium chlorid by mouth increased the acidity of the blood as had been previously shown by Gamble, Ross, and Tisdall. Calcium lactate was without effect. Calcium chlorid intravenously did not cause an acidosis; the calcium not being excreted in the feces or urine.

HIGGINS, Cincinnati.

COLLOIDAL STABILITY OF THE SERUM AND INFECTIONS. LEO MENDEL, Jahrb. f. Kinderh. **106**:15, 1924.

Results with Daranyi's reaction do not support claims of its value in the diagnosis of tuberculosis, because almost any severe infection may give a positive result. Severe catarrhal infections regularly caused a loss of colloidal stability of the serum; milder infections, such as bronchitis and pharyngitis, caused a loss of stability with the return of normal temperature. In whooping cough and congenital syphilis the reaction was variable but with no relation to the clinical picture.

A NEW CULTURE METHOD FOR B. BIFIDUS AND ACIDOPHILUS WITH ANAEROBIC SURFACE GROWTH. REINHOLD RÜHLE, Jahrb. f. Kinderh. **106**:21, 1924.

Cultures from the breast were streaked on plates of Loeffler's medium, the plate being inverted over a Petri dish of the same size with a gummed edge, containing pyrogallic acid and sodium hydroxid. After two days similar subcultures were made, in which *B. bifidus* and *acidophilus* were practically always in separate colonies instead of being mixed as is usually the case when other methods are used.

PIN-SHAPED BACTERIA OF MECONIUM. E. SCHÜSSLER, Jahrb. f. Kinderh. **106**:33, 1924.

The status of the pin-shaped bacterium, described in the meconium by Escherich in 1886, has never been decided. The four cultures which the author isolated from 112 specimens of meconium were decided to be degeneration forms of *B. amylobacter*. These organisms grow in liver bouillon, coagulate but do not peptonize milk, do not liquefy gelatin, do not blacken brain pulp and in Zetrow preparation have regular peritrichal flagella. The spores do not resist heat for more than ten minutes, and the cultures are not pathogenic to guinea-pigs.

SUTHERLAND, Chicago.

FLAGELLAR AGGLUTININS. MARION L. ORCUTT, J. Exper. Med. **40**:43, 1924.

By means of two groups of experiments, one dealing with a change in motility occurring without one strain of bacilli and the accompanying change in serologic behavior, and the other dealing with artificial separation of the flagellae from the bodies of bacilli and the direct production of a flagellar antiserum which agglutinates exclusively the motile bacilli the author confirms the earlier work and furnishes more evidence which proves the existence of flagellae as a separate antigenic factor giving rise to a specific agglutinin.

The authors' conclusions are:

1. Certain bacilli within one strain may lose their flagellae and become nonmotile.
2. The change in serologic behavior associated with the change in motility indicates that the flagellae possess an individual antigenic property.
3. Flagellae can be separated from the bodies of the bacilli.
4. A strictly flagellar antiserum can be produced by the injection of a flagellar suspension.
5. This direct production of a strictly flagellar antiserum is proof of the existence in flagellae of a separate specific antigen.

CAUSE OF IMMEDIATE DEATH BY LARGE DOSES OF BOTULINUS TOXIN. JACQUES J. BRONFENBRENNER, MONROE J. SCHLESINGER and PAUL F. ORR, J. Exper. Med. **40**:81, 1924.

One of the authors (Orr) has observed that injection of massive doses of food products experimentally infected with *Bacillus botulinus* may cause the death of animals in from five to ten minutes. This apparent absence of an incubation period, being inconsistent with the established conception of the mode of action of bacterial toxins, lead to the present study.

Diluted filtrates of meat glucose broth cultures of *B. botulinus* Type A, were injected intraperitoneally into mice. Large doses of the filtrate killed them almost immediately. The authors attribute this rapid action to a chemical poison having properties distinct from those of botulinus toxin. The poison is not neutralized by botulinus antitoxin, is thermostabile but if heated in an open container its toxicity is diminished with a coincidental volatilization of basic material. The volatile substance can be identified as ammonia.

Death resulting from injection of small quantities of ammonium salts may be delayed sufficiently long to suggest a period of incubation similar to that found in botulism. In testing partly decomposed food for botulinus toxin, it is conceivable that it may be contaminated with common putrefactive bacteria yielding ammonia and thus cause the death of the test animals. If test mice protected with botulinus antitoxin are used in addition to normal ones, chances of error in interpretation of results will be reduced, though not ruled out.

Test of the thermostability of the toxic constituents of suspected food may conceivably help to determine the true nature of the poison.

McCLURE, Evanston, Ill.

STUDIES IN BACTERIAL METABOLISM. LXX. MICROCOCCUS OVALIS. ARTHUR ISAAC KENDALL and REBA CORDELIA HANER, J. Infect. Dis. **35**:67 (July) 1924.

A study of the metabolism of a strain of *Micrococcus ovalis* was made to determine the nature of the nitrogenous interchange of the organisms with the nutritive environment.

The observations made would seem to justify the belief that *Micrococcus ovalis* and its variants are normal intestinal microbes of the obligate, or nearly obligate lactic acid forming type. Their restriction to the upper segments of the intestinal tract in the nursling, and artificially fed child, is not wholly clear, although current information justifies this statement. In the adult, how-

ever, the duodenal habitat can be definitely associated with the dietary status of the host. In this region, but not necessarily below, available carbohydrate is practically always present if the host is enjoying a mixed diet. The relatively rapid absorption of carbohydrate from the lower levels of the intestinal tract results in a protein rich carbohydrate-free intestinal content, which is unfavorable for the development of the enterococcus.

STUDIES IN BACTERIAL METABOLISM. LXXI. BACILLUS BIFIDUS. ARTHUR ISAAC KENDALL and REBA CORDELIA HANER, J. Infect. Dis. **37:** (July) 1924.

A study of the nitrogenous metabolism was made of three strains of *B. bifidus,* using methods previously reported.

It was found that *B. bifidus,* and its variants, is an anaerobic organism exhibiting distinct tendencies toward pleomorphism in artificial cultural mediums, especially lactose. It is inert, both culturally and chemically, in mediums containing proteins or protein derivatives, without utilizable carbohydrate. In the presence of the latter, however, it produces considerable amounts of organic acids, chiefly lactic.

It has no discernible action on amino-acids containing aromatic nuclei, which makes it theoretically at least a suitable microbe for intestinal implantation and diet therapy. Its occurrence in the intestinal contents and feces of normal nurslings is significant in this respect, but the difficulties of isolation and cultivation do not characterize it as an economic competitor of *B. acidophilus.* From the chemical point of view, the disproportionate action of the bifidus group on the galactose glucosid configuration offers a rather striking contrast to the members of the acidophilus group, which seem to utilize the glucose glucosid configuration to better advantage.

STUDIES IN BACTERIAL METABOLISM. LXXII. BACILLUS ACIDOPHILUS. ARTHUR ISAAC KENDALL and REBA CORDELIA HANER, J. Infect. Dis. **35**:89 (July) 1924.

An attempt was made to determine whether the products of metabolism of *B. acidophilus* implanted in the intestinal tract would be beneficial, neutral or harmful. The various types were cultivated in mediums which are representative in type, if not in detail, of those which may be found within the alimentary canal of man.

The results of this study have corroborated ideas of the qualitative fermentative reactions of the aciduric group so far as available evidence shows, and more important, have revealed the singularly negative character of their nitrogenous metabolism, characteristic of the obligately fermentative types of naturally occurring intestinal microbes. This is significant in light of the relation between a carbohydrate rich, protein poor diet, which encourages the aciduric group in the human intestinal tract, and the nature of the regimen which must be pursued to induce successful growths of acidophili in an implantation therapy.

The conclusion is reached that the secret of acidophilic and other lactic acid therapy is not to emphasize the administration of the microbe, but to regard the proliferation of the microbe in the intestinal tract merely as an indication of the establishment of a correct and successful regimen. From the point of view of the host, the dietary condition in the alimentary canal rather than the microbe is the goal to attain.

KENNEDY, Rochester, Minn.

THE INFLUENCE OF SUNLIGHT UPON THE BACTERICIDAL POWER OF HUMAN BLOOD. LEONARD COLEBROOK, Brit. M. A. J. **11**:3314, 1924.

The author conducted interesting experiments in the Alps, in which he exposed two men for one hour to the noonday sun, one a healthy man and the other one in poor health. Examination of the blood following this sun

bath showed that the bactericidal or killing power of the blood in the normal person had been materially increased while the result in the delicate man was the reverse. He argues that the possible benefit from sun cures in tuberculosis and other infections may be due to this increased killing power of the blood. The observer correctly utters a word of warning relative to the very ill patients not responding favorably to the sunlight or arc treatment, viz., that the leukocytes which are functioning badly are easily harmed by the action of light on the skin, while those which are functioning well are tolerant of large doses and respond to these large doses by exhibiting a still greater activity.

BROWN, Toronto.

ON THE REDUCTION OF THE BACTERICIDAL POWER OF BLOOD, WHICH IS EFFECTED BY ADDING TO IT CITRATE OF SODA AND OTHER DECALCIFYING AGENTS; AND ON THE QUESTION OF WHETHER BLOOD SO TREATED SHOULD BE EMPLOYED FOR IMMUNOTRANSFUSION. LEONARD COLEBROOK and E. J. STORER, Brit. J. Exper. Pathol. **5**:47, 1924.

The addition of 0.25 per cent. sodium oxalate, as well as ammonium oxalate or sodium phosphate, to the blood of either a normal person or one who had shown an immunizing response to vaccine injection, caused a decrease in bactericidal power against staphylococcus and streptococcus, but practically no change in the opsonic power of the plasma. They therefore believe this loss in bactericidal power to be due to an interference with the functions of the leukocytes, and recommend that citrated blood should not be employed for "immunotransfusion."

HOAG, New York.

OBSERVATIONS ON THE EFFECT OF FREEZIN ON DIPHTHERIA TOXIN ANTITOXIN MIXTURES. MARY B. KIRKBRIDE and JESSIE E. DAW, J. A. M. A. **82**:1678, 1924.

In one-tenth L+ and L+ mixtures of toxin antitoxin toxicity tests were made on guinea-pigs. The mixtures were exposed to temperatures below freezing of approximately 22 F. from 16 to 20 F., and 0 F. for very short periods and for periods of three, eighteen, twenty-four, and seventy-two hours. The intervals between the time at which the samples had become melted and their injection were varied. To ascertain whether any difference in toxicity could be detected from mixtures in which the precipitate, which forms on exposure to freezing temperatures, was in suspension or had largely settled out, tests were made with the cloudy material and with the clear supernatant fluid.

Whereas control samples of mixtures injected in 5.0 c.c. amounts into guinea-pigs induced moderate to severe local reactions and late paralysis with death, the frozen mixtures produced quite generally a much milder reaction. Unfortunately an epizootic infection occurred during the experiments. Some of the deaths attributed to the infection may have been influenced by the frozen toxin antitoxin mixtures. The authors conclude that under the usual tests of toxicity there is no evidence of increased toxicity of the mixtures, which can be attributed to dissociation of the toxin and the antitoxin as a result of freezing.

EFFECT OF EXPOSURE TO LOW TEMPERATURES ON DIPHTHERIA TOXIN ANTITOXIN MIXTURE. BENJAMIN WHITE and ELLIOTT ROBINSON, J. A. M. A. **82**:1675, 1924.

It was found that the exposure of one L+ and toxin-antitoxin mixtures to temperatures of 10 F. or less, for periods of six hours or more causes a turbidity which arises from the separation and precipitation of antitoxin and possibly other substances which results in an increase in the toxicity of these

mixtures. This toxicity is due to the dissociation of the toxin and antitoxin combination. With this dissociation, a part at least of the antitoxin becomes insoluble and it therefore no longer possesses its full neutralizing power. This condition results in the presence in the solution of an increased proportion of free toxin.

EFFECT OF FREEZING ON DIPHTHERIA TOXIN ANTITOXIN MIXTURES, AS REGARDS TOXICITY. JOHN F. ANDERSON and GEORGE F. LEONARD, J. A. M. A. **82**:1679, 1924.

In different lots of diphtheria toxin antitoxin mixtures, both three L + and one-tenth L + doses of toxin were tested before and after freezing. The various lots were frozen for periods varying from eighteen to ninety-six hours at temperatures slightly below freezing to 5 C. Effects of different preservatives were also tried.

It was found that in no instance was there an increase in toxicity after freezing of mixtures of diphtheria toxin antitoxin made with a refined antitoxin or globulin, according either to the old or new formula.

Freezing of a 3 L + dose mixture of toxin antitoxin containing 0.3 per cent. tricresol, prepared with an antitoxin concentrated without the use of heat, or an unconcentrated antitoxin, resulted in an increase in toxicity of the mixture.

Freezing of such mixtures in which chlorbutanol or chloroform is used as a preservative or in which no preservative is used, does not cause an increase in toxicity of the mixture.

Anderson and Leonard recommend that only highly refined antitoxin or globulin should be used in the preparation of diphtheria toxin antitoxin mixtures, and that only mixtures containing one-tenth L + doses should be permitted.

HENN, Chicago.

Nutrition

DIET AND TISSUE GROWTH. I. THE REGENERATION OF LIVER TISSUE ON VARIOUS ADEQUATE DIETS. THEODORE S. MOISE and ARTHUR H. SMITH, J. Exper. Med. **40**:13, 1924.

It seems reasonable to suppose that the optimal nutritive conditions for growth of the body as a whole are similar to those necessary for reconstruction of one of its constituent parts. The determination of the best conditions for rapid healing of wounds is of practical importance in surgery, and a study of diet and tissue regeneration might also throw valuable sidelights on growth.

A group of white rats was placed on each of the following diets: a normal balanced diet, a high fat diet, a high carbohydrate diet, and a high protein diet. The diets were begun soon after weaning, and continued until the rats had grown to 80 and 100 gm., when the liver tissue was injured by subcutaneous injection of chloroform in sterile mineral oil. Rats of each group were killed with artificial illuminating gas at twenty-four hour intervals up to 144 hours after the administration of the chloroform, and the livers were immediately removed and fixed.

The toxicity of chloroform varies according to the diets used in these experiments in the following order of decreasing susceptibility of the animals: high fat > standard > high carbohydrate > high protein diets.

The most active and rapid repair is observed on the standard balanced diet. On high fat diet the reparative process is definitely delayed in comparison with the other diets. Only slight differences are observed between the high carbohydrate and high protein diets, which suggest but do not conclusively show a more rapid repair with the latter diet.

MCCLURE, Evanston, Ill.

THE NUTRITIONAL REQUIREMENTS OF BABY CHICKS. IV. THE CHICKS' REQUIREMENT FOR VITAMIN A. E. B. HART, H. STEENBOCK, S. LEPOVSKY and J. G. HALPIN, J. Biol. Chem. **60**:341, 1924.

The authors have experimented with Plymouth Rock Chickens on diets without vitamin A and found growth was greatly retarded. This is contrary to the findings of Sugiura and Benedict that "fat-soluble vitamin is not essential in any stage of avian nutrition."

HIGGINS, Cincinnati.

THE INFLUENCE OF MINERAL DEFICIENCY IN GOAT'S MILK ON THE SKELETAL GROWTH OF KIDS. S. V. TELFER and J. A. CRICHTON, Brit. J. Exper. Pathol. **5**:84, 1924.

A pair of kids fed on unaltered goat's milk from the age of 10 days showed normal development. A 15 per cent. reduction of the mineral content induced a considerable osteoporosis in another pair of kids, but allowed normal gain in weight. A reduction in mineral content of about 20 per cent. although allowing an initial period of growth, was followed not only by markedly defective ossification, but also signs of impaired general nutrition. On the other hand, a 70 per cent. increase of the normally proportioned ash caused a rate of ossification greater than that in the control animals. They believe the amount of mineral constituents in the milk of a certain species bears a close relation to the rate of growth in the young of that species, and that the amount is near the minimal requirements.

HOAG, New York.

THE VALUE OF MILK ACIDIFIED WITH LEMON JUICE; ITS COMBINATION WITH EGG YOLKS TO ADD THE ANTIRACHITIC FACTOR. ALFRED F. HESS and MILTON J. MATZNER, J. A. M. A. **82**:1604, 1924.

Lemon juice added to cow's milk in proportion of 21 c.c. to a quart of milk, reduces buffer action and increases the hydrogen-ion concentration from p_H 6.64 to about 5.54. In this way it is thought that cow's milk is rendered more digestible and its true acidity in the stomach is made to resemble more nearly that of human milk. Infants who received milk prepared with lemon juice throve well for long periods.

Lemon juice has been added to cow's milk with the same object in view, as has been the addition of lactic acid or hydrochloric acid. The advantage of lemon juice is that it supplies antiscorbutic vitamin. The advantage of lemon juice over orange or tomato juice is that in small quantities it will increase the hydrogen-ion concentration without curdling the milk. Egg yolk can be combined with the mixture of lemon juice and milk with but slight alteration of the hydrogen-ion concentration. In this manner there is a combination that is well borne by infants and there is furnished both the antiscorbutic and antirachitic factors, as well as fat-soluble vitamin and iron.

HENN, Chicago.

DEFICIENCY DISEASES, WITH SPECIAL REFERENCE TO RICKETS. EDWARD MELLANBY, Brit. M. J. **1**:895, 1924.

The author, in his lecture before the Bradford Division of the British Medical Association gives a good summary of the situation under the following headings: 1. Fat soluble vitamin and the bone abnormalities of rickets and osteoporosis. 2. The interaction of cereals and antirachitic vitamin. 3. The effect of fat soluble vitamin and other dietetic factors on the structure of teeth. 4. Fat soluble vitamins and muscle structure and function. 5. Relation of light radiations to deficiency disease. 6. Malnutrition and wasting of infants. Mellanby in his discourse carefully distinguishes between vitamin A and the antirachitic factor, the former he employs in referring to growth and kerato-

malacia. Under heading (1) he cites the interesting observation that the separation of butter from milk spoils both products from the point of view of antirachitic effect; to get the best antirachitic effect from butter, extra calcium in the form of calcium carbonate should be added to the diet. Regarding the antirachitic effect of cow's milk he cites the fact that 2 c.c. of pasture-fed cow's milk has the same antirachitic effect as 15 c.c. of milk from the same cow fed on white maize meal, gluten meal, oats and barley, and kept in a dark stall. Of great importance is the supplying of ample antirachitic factors to the pregnant woman. This he believes essential in establishing, so to speak, an antirachitic child. These observations were conducted on pregnant bitches. Regarding the second heading he makes a most practical observation in the relation of cereals to the antirachitic factor. Rapid growth naturally entails more bone calcification, and hence the more need for dietetic factors stimulating bone calcification. Cereals, and especially oatmeal, possess this anticalcification effect, presumably because they contain some anticalcifying substance. Milk, egg-yolk and butter offset this effect. In other words, the more cereal eaten and the more potent the cereal (oatmeal) so far as producing rickets is concerned the greater must be the antirachitic factors to produce normal development. Under the third heading the interesting observation was made that on microscopic examination 85 per cent. of supposedly normal teeth contained defective structure, Mellanby contends, as a result of defective diet during the formative period, from the antirachitic standpoint; he further points out that this defective growth of the teeth in utero produces fertile field for the development of caries later on. In the third portion of his paper he states that a defective (in fat soluble vitamin) diet containing excess cereal is capable of producing muscles which are extraordinarily defective in structure and have the appearance of pseudomuscular dystrophy, in other words, he believes that the diet controls the activity of the person. Nature, he says, has so arranged things that a strong active muscle is developed along with a well calcified bone. Under the fourth heading he concludes that sunlight and ultra violet radiations "increase the effectiveness of fat soluble vitamin in the body, and thereby improve the nutritional value of moderately defective diets. A good diet can more than counterbalance darkness or absence of ultra violet influence but sunlight cannot make up for a really defective diet." Mellanby's application of his experimental data to artificial feeding of infants is interesting. The older feeding methods of Czerny and Finkelstein must now be put in the discard, according to the author's ideas. Any method of feeding sick children which calls for removing or reducing of the vitamins must, in Mellanby's opinion, be wrong, he questions the existence of fat indigestion and states that reduction in the fat qua fat is probably of but little importance in the nutrition of children so long as they get sufficient food to eat, but if its vitamin content goes with it, then ultimately further ill health will ensue. Thus if fat is reduced or removed, he feels that this reduction should be replaced by either egg yolk or cod liver oil. The diet recommended for a three months infant is most illuminating: milk, 16 ounces; water, 8 ounces; four egg yolks; cod liver oil, 4 drams; orange juice, 4 drams. Professor Mellanby fails to recognize that babies are not animals, and that for the successful feeding of well or sick infants many other factors must be considered other than true scientific principles.

BROWN, Toronto.

STUDIES IN SCURVY. I. THE ANTISCORBUTIC VALUE OF CERTAIN VEGETABLE PRODUCTS. J. AXEL HÖJER, Supplement, Acta Pediat. **3**:18 (May) 1924.

The author tested a number of fruits and vegetables for their antiscorbutic content. A great variation was found in the potency of products grown in different seasons. Uniformly low values were found for all products raised in the summer of 1922 when there was little sunshine, from which the author concludes the sunshine is essential for the production of vitamin C.

II. Histopathologic Studies in Scurvy. Ibid., p. 29.

In this very extensive study, conducted largely on guinea-pigs, the author finds pathologic changes much more widespread than have been described previously. Atrophic changes in the muscles, lymphoid tissue, liver, salivary glands, suprarenal and kidney are constantly found. Generalized atrophy of connective tissue, particularly of its collagen fibrils, is most striking. The marked changes in the bones and teeth are generally misinterpreted. The author describes an intermediate stage of abnormal bone and tooth formation, produced by the injury to the osteoblast and odontoblast before their activity finally ceases. The changes are not due to hemorrhage but to impaired cellular activity caused by lack of antiscorbutic. The hemorrhages that occur can generally be attributed to a deficiency of collagen fibrils in the vessel walls.

III. Some Scurvy Problems. Ibid., p. 115.

Concerning the relation of scurvy to infections, the author shows that infections may aggravate scurvy. Local inflammation may induce hemorrhages, causing a weakened vessel wall to give way. Gastro-intestinal disturbances, especially diarrheas, tend to produce scurvy by interfering with the absorption of antiscorbutic from the intestine. On the other hand, scurvy renders the organism more susceptible to infections, (1) by causing an atrophy of lymphoid tissue; (2) by lowering resistance in individual organs in the vicinity of scorbutic lesions.

Concerning the nature of the effect of antiscorbutics on the body cells, the author concludes that the theory of Abderbalden and Wertheimer that antiscorbutics assist oxidative processes is supported by the known facts. In his own material he finds marked changes in the nuclei of cells which, according to Loeb, govern physiologic oxidations.

IV. The Relation of Scurvy to Tuberculosis. Ibid., p. 140.

Animal and human experiments were conducted on this question. Guinea-pigs on scorbutic and antiscorbutic diets were injected with tubercle bacilli. Those without scurvy lived longer and usually showed less extensive tubercles at necropsy. The histologic picture was essentially different in that the animals with scurvy showed a much more limited connective tissue reaction about their tubercles. Defective collagen fibrils were very noticeable.

The human experiments were conducted in a sanatorium at a time of year when the normal diet was comparatively low in antiscorbutic. A series of patients who were given daily additional orange juice showed much more favorable progress than a control series. The conclusion is drawn that even latent scurvy exercises an unfavorable influence on the course of tuberculosis.

Holt, Baltimore.

Diseases of the New-Born

Rate of Sugar Absorption in the New-Born. Randolph G. Flood, J. A. M. A. **82**:1595, 1924.

Flood has plotted the blood sugar curves of a limited number of infants under 14 days of age, following the ingestion by gavage of glucose, maltose, lactose, galactose, levulose, and sucrose. The disaccharids show some of the characteristics of their component monosaccharids. In order of rapidity of absorption the sugars ranked as before mentioned. The Folin-Wu method of blood sugar determination was used, with the exception that only 2.0 c.c. of blood was employed for each test.

Henn, Chicago.

Acute Infections

ROENTGEN-RAY THERAPY OF POLIOMYELITIS. HERMAN B. PHILIP and WALTER I. GALLAND, J. A. M. A. **82**:1847, 1924.

The types of poliomyelitis cases treated were divided into two general classes, one, in which the stimulation of the diseased anterior horn cells was desired, with the objective of improvement in the paralysis, and a second, in which the irradiation was given to overcome the persistent hyperesthesia so far unresponsive to any form of therapy.

The doses used have been stimulating only. Treatments were given at weekly intervals, exposures were made alternately on the anterior and posterior surfaces of the body at the level of the involved spinal segments.

In three cases of paralysis there was apparently an improvement following irradiation. In four other cases, where hyperesthesia was pronounced, improvement was noted within a week after treatment.

The authors feel that roentgen-ray therapy offers a method of shortening the period of hyperesthesia following the acute stage of poliomyelitis, and that such therapy offers a safe and early applied method of stimulating diseased but viable anterior horn cells in poliomyelitis in the stationary stage.

FATAL HEMORRHAGE FOLLOWING TRACHEOTOMY FOR LARYNGEAL DIPHTHERIA. KARL SCHLAEPFER, J. A. M. A. **82**:1581, 1924.

Two cases of deaths are reported from hemorrhage of the innominate artery in children whose tracheotomy wounds had become infected. The deaths occurred nine and seventeen days after operation. Of 115 cases of hemorrhage reviewed in the literature by the author, the source was found in the innominate artery in eighty-three patients; in the common carotid artery in five; in the inferior thyroid artery in three; in the superior thyroid artery in one; in aortic aneurysms in two; in the right innominate vein in four, and in seventeen the source was not reported.

Fatal hemorrhage may occur days, weeks or months following tracheotomy for laryngeal diphtheria, if the wall of a larger blood vessel is injured at the time of operation.

Schlaepfer makes suggestions for avoiding this complication by the use of blunt retractors, coverered with gauze, avoiding marked retraction of the head, and in inferior tracheotomy by paying special attention to the innominate artery. The incision should be made from below upward, for this renders mechanical injury to the walls of the innominate vessels less probable.

IMMUNIZATION OF CHILDREN AGAINST FLEXNER DYSENTERY. LAWSON WILKINS and H. S. WELLS, J. A. M. A. **82**:1599, 1924.

In an institution where Flexner dysentery had been present during several summers prior to 1923, a vaccine was employed after the usual measures had failed to check the disease.

Seventy children were inoculated with a monovalent Flexner vaccine made from a strain isolated from one of the patients. Three doses of 250, 500 and 1,000 million, respectively, were given subcutaneously. Only two had general reactions, which were attributed to improper preservation of the vaccine. The local reactions were mild.

Whereas the usual measures had failed to prevent the spread of the disease; in two months' time, after vaccination, only one child developed dysentery. In this child it was found that the vaccines had produced no agglutinins. The other children, tested six weeks after vaccination, had definite agglutinins.

Definite conclusions cannot be drawn from a single series but the results were sufficiently encouraging to warrant further attempts of this kind.

HENN, Chicago.

EPIDEMIC ENCEPHALITIS TREATED WITH MERCUROCHROME-220 SOLUBLE. JOHN W. VISHER, Northwest Med. **23**:271 (June) 1924.

Visher reports two cases, the first in a boy, aged 16, who developed encephalitis following measles, the second in a man, aged 51, in whom the condition was apparently primary. The first patient received two doses of 1 per cent. mercurochrome-220 soluble, 10 and 8 c.c. respectively, given in freshly distilled water, the second patient received one dose of 10 c.c. of 1 per cent. solution. Rapid clearing of symptoms occurred in both following this medication. The drug was given intravenously, 10 c.c. being given in three minutes.

SCOTT, Philadelphia.

THE CRITICAL THREE DAY FEVER, AN EXANTHEM OF YOUNG CHILDREN (EXANTHEMA SUBITUM). E. GLANZMANN, Schweiz. med. Wchnschr. **54**: (June 26) 1924.

Zahorsky, in 1910, was the first to call attention to an exanthem which he preferred to name Roseola Infantilis (or infantum). In 1913 he was able to say he had seen thirty-three cases. Among those who also published articles on the subject may be included Wescott, 1921; Veeder and Hempelmann, 1921, who noted that the typical blood picture was a leukopenia with a relative lymphocytosis and who gave the malady the name "Exanthema Subitum"; Greenthal, 1922; Park and Michael, 1922; Ruh and Garvin, 1923.

The author of this paper has seen cases in Bern since 1918. His observations coincide essentially with those of the American authors who first published accounts of the disease: namely, that it is an exanthem which occurs especially between the sixth and twenty-fourth months, the onset taking place suddenly with no prodromes. For three days there is a high fever (from 103 to 105) and on the morning of the fourth day the temperature falls by crisis, a few hours subsequently appears a rash, morbilliform and macular in character. The blood picture is as described in the foregoing. He noted no glandular involvement, very slight gastro-intestinal derangement and no complications, no sequelae.

ELTERICH, JR., Pittsburgh.

THE TREATMENT OF SCARLET FEVER WITH DOCHEZ'S ANTISCARLATINAL SERUM. FRANCIS G. BLAKE, Boston M. & S. J. **191**:44 (July 10) 1924.

Besides the thirteen cases in the preliminary report of Blake, Truck, and Lynch, the results in thirteen additional cases of scarlet fever treated with Dochez's scarlatinal antistreptococcic serum are given. Of the twenty-six cases, twenty were early uncomplicated cases treated on or before the fourth day of the disease, and six were cases with septic complications. There was one death, an extremely toxic and septic patient with ulcerative tonsillitis, bull neck, thrombophlebitis, and streptococcus septicemia, receiving a single injection of 40 c.c. on the fifth day of the disease without benefit.

These investigations apparently show (1) that a specific toxin or toxic substance is present in the blood in scarlet fever, (2) that the toxic substance disappears from the blood promptly after serum treatment with rapid clinical cure as evidenced by critical fall of temperature and pulse to normal, rapid fading of the exanthem, and prompt return to a state of well being, and (3) that the serum of the treated patient acquires the capacity to produce a positive Schultz-Charlton rash extinction test within a few hours after intramuscular injection of Dochez's serum, a capacity which is not ordinarily acquired until comparatively late in convalescence.

GENGENBACH, Denver.

THE MYOCARDIAL LESIONS OF DIPHTHERIA. ALFRED SCOTT WARTHIN, J. Infect. Dis. **35**:32 (July) 1924.

Warthin states that there is a disagreement in the interpretation of pathologic findings and in the correlation of these with physiologic phenomena which occur in the heart in cases of diphtheria. In the attempt to clear up some of these questions, he studied hearts from sixteen necropsy cases of diphtheria.

He found that the essential lesion of the heart in diphtheria is a toxic parenchymatous hyalin degeneration or necrosis, associated frequently with fatty degenerative infiltration and less frequently with cloudy swelling or a simple necrosis. The latter lesions are most probably due to accompanying nutritional conditions. Following the lesion, there is (if the patient survives) a reparative inflammatory process (myocarditis) accompanied by muscle regeneration. Either a complete regeneration or a fibrosis may result. The toxin of diphtheria may damage the conducting mechanism as well as the muscle fibers. Pathologically no especial affinity is shown for either apparatus.

KENNEDY, Rochester, Minn.

Chronic Infections

QUANTITATIVE STUDIES IN SYPHILIS FROM A CLINICAL AND BIOLOGIC POINT OF VIEW. XIV. LOCALIZATION AND FATE OF ARSPHENAMIN, NEO-ARSPHENAMIN, SILVER ARSPHENAMIN, TRYPARSAMIDE IN THE VISCERA AFTER INTRAVENOUS ADMINISTRATION IN RATS. JOHN A. FORDYCE; ISADORE ROSEN, and C. N. MEYERS, Am. J. Syphilis **8**:377, 1924.

A single dose about twenty times the clinical dose per kilogram was given, and the arsenic content of the blood, liver, spleen and kidneys and brain determined at intervals of from seven seconds to seven days. The results indicate that there are other storage places than these examined. In general, the most arsenic was present on the first and second days, and then gradually decreased but was far from normal in seven days. Arsphenamin showed greater permeability for the brain than any of the other arsenicals, while tryparsamide did not show the high permeability as claimed.

SERUM DIAGNOSIS OF ACTIVE TUBERCULOSIS. W. HELLMANN, Jahrb. f. Kinderh. **106**:1, 1924.

The serum from nine of fifteen individuals with active tuberculosis agglutinated specially treated tubercle bacilli in dilutions of 1:100 or more. Normal guinea-pigs, and rabbits, normal infants and children with latent tuberculosis showed a reaction in dilutions from 1:10 to 1:80. The agglutination was in general parallel with the tuberculin reaction and the clinical findings. The author concluded that an agglutination reaction in the dilution of 1:100 or more was a strong indication of an active tuberculous process, though agglutination only in more concentrated solutions was not incompatible with an active process.

SUTHERLAND, Chicago.

TUBERCULOSIS IN CHILDREN. HENRY D. CHADWICK, Boston M. & S. J. **191**:58 (July 10) 1924.

The author emphasizes the rate of growth as a criterion of health in children; that in school children, 8 per cent. of those under weight showed evidence of tuberculosis; that a school child 10 per cent. under weight has lost about one year of normal growth; that the first symptom of tuberculosis in children is fatigue rather than cough; that some children may normally have temperature up to 99.6 in the afternoon without having fever or tuberculosis.

GENGENBACH. Denver.

TUBERCULOSIS IN INFANTS. OSCAR M. SCHLOSS, Southern M. J. **17**:474, 1924.

Tuberculosis in infants can be divided into three stages: primary, secondary and tertiary. The secondary stage is the important one. From the focal lesions of the secondary stage originate the so-called tertiary lesions which form the clinically recognizable forms of tuberculosis. The secondary lesions always develop from the primary lesion.

The enteric form of tuberculosis is in most instances due to the bovine bacillus and is usually a milk-born infection.

Certified milk may not be as safe as one would assume. The animal could become infected between tests, or the reactivity to tuberculin of an infected animal could wilfully be suppressed by giving a large dose of tuberculin.

If the large mortality of tuberculosis in infants is to be controlled the disease must be recognized in its secondary or glandular stage.

Aid in diagnosis is the history. There is a period during which the infant who previously throve well did not do so well. There was failure to gain and definite pallor. Slight rises of temperature are commonly found. In many cases there is a history of chronic cough. Symptoms somewhat similar, with the exception of cough, are found in the enteric type.

The nutrition of such infants may be little impaired even after the secondary stage has merged into the third.

Physical signs are unfortunately hardly present during the second stage.

The tuberculin test and the roentgen ray are the two most reliable means of diagnosis. The author depends more on the intracutaneous test of tuberculin than the cutaneous.

The prognosis in infantile tuberculosis is not necessarily bad if the disease can be recognized before the tertiary stage is reached and if appropriate therapeutic procedure can be promptly and effectively instituted.

SCHLUTZ, Minneapolis.

Internal Diseases

GASTRO-INTESTINAL BLEEDING IN ASTHMA AND OTHER FORMS OF ALLERGY. WILLIAM LINTZ, Boston M. & S. J. **190**:980 (June 5) 1924.

Although the cases under observation were apparently adults, and while gastric and duodenal ulcers are rather uncommon in childhood, yet it might be well to recognize the danger of mistaking blood in stomach contents and stools occurring in some form of allergy as being due to some organic condition.

REPORT OF AN ACUTE LUNG ABSCESS IN A CHILD CURED BY ARTIFICIAL PNEUMOTHORAX. GERARDO BALBOUR and EDWARD D. CHURCHILL, Boston M. & S. J. **190**:965 (June 5) 1924.

An interesting case of post-tonsillectomy abscess of the left lung in a Syrian girl, aged 8 years, which spontaneously ruptured into a bronchus, and was apparently completely cured by artificial pneumothorax. Only one injection of 450 c.c. of air was given.

Interesting roentgen-ray reproductions accompany the article. In looking up the literature, out of one hundred cases of lung abscess treated by pneumothorax, the authors found only three cases reported in children under 12 years, although J. B. Murphy, in 1898 advocated collapse of the lung in abscesses without adhesions and with bronchial communications. A summary of the three cases previously reported is given.

GENGENBACH, Denver.

PATHOGENESIS OF ALIMENTARY ANEMIA. FRITZ LIEBENSTEIN, Jahrb. f. Kinderh. **106**:39, 1924.

Extracts of feces were made by Seyderhelm's method, and the extract injected intravenously in rabbits. Stools of breast fed infants were entirely nontoxic when studied in this way, while the stools of artificially fed infants whether healthy or ill, had a decidedly toxic action on the spinal cord, and a distinct tendency to produce anemia. Similar results were obtained when extracts were made of pure cultures of streptobacilli and *B. coli.*

TREATMENT OF DYSPEPSIA. JESTER, Jahrb. f. Kinderh. **106**:51, 1924.

The author reports good results with a preparation of lactic acid and calcium bilactate which was added to the milk formula. A fine coagulum was produced in the milk. Vomiting resulted in a few cases. Sugar was added to overcome the sour taste. Aside from possible simplicity in the preparation, this would seem to have no advantage over lactic acid or albumin milk.

SUTHERLAND, Chicago.

EVENTRATION OF THE DIAPHRAGM. HENRY J. WALTON, Am. J. Roentgenol. **2**:420 (May) 1924.

In contrast to diaphragmatic hernia one dome of the diaphragm is stretched so that the underlying viscera are contained within the thorax. It is four times as frequent in the male and is generally on the left side. It is regarded as a congenital defect, but before roentgenographic examinations was a necropsy discovery.

In the differential diagnosis pleural effusion, pneumothorax and hernia of the diaphragm are considered, and the two former are eliminated by barium meal and enema.

The important roentgenographic signs are (1) the high diaphragmatic arch; (2) the regular contour of the arched line; (3) positive though limited excursion; (4) paradoxical movement on affected side; (5) mediastinal excursion from affected side toward the sound side during inspiration; (6) displacement of heart to right; (7) distinguishing line between diaphragm and viscera below and pneumoperitoneum. The only pathognomonic sign is the distinguishable separation of the arched dome, and the viscera visible only after introducing air into the peritoneal cavity.

The reported case had besides the left eventration a transposition of liver (congenital defect) and dextrocardia.

Eventration may not be as rare as previously considered.

A CASE OF HODGKIN'S DISEASE, WITH LATE DEVELOPMENT OF SACROILIAC DISEASE, CURED BY ROENTGEN-RAY TREATMENT. G. E. PFAHLER and C. P. O'BOYLE, Am. J. Roentgenol. **2**:406 (May) 1924.

A girl, aged 16, had large glandular masses in both sides of neck, axillae, and as showin by roentgenogram, in the mediastinum, which on section showed Hodgkin's disease. After five applications of the roentgen ray over a period of eighteen months, the clinical cure included reappearance of menses in spite of two abdominal ray treatments. One year after stopping treatments a tumor mass developed over the left hip. A roentgenogram showed a tumor mass of soft tissue density and a destructive disease of the left sacroiliac joint with adjacent atrophy. No glandular enlargement had reappeared and the new focus did not resemble tuberculosis. The roentgen ray was applied and in a month the joint was healed and the gluteal abscess gone. If this secondary focus was Hodgkin's the rapid disappearance was to be expected, but if tuberculous we

have an argument for early roentgen-ray treatment of bone or joint tuberculosis.

In the discussion, Holmes cites a secondary spinal canal growth producing severe pain which on operation proved to be an Hodgkin's enlargement.

Pancoast described a sudden exophthalmus which disappeared after radiation, and he regards herpes zoster as a complication of Hodgkin's disease due to nerve pressure. Accurate diagnosis should be made by biopsy by a competent pathologist.

STULIK, Chicago.

HIRSCHSPRUNG'S DISEASE. DONALD V. TRUEBLOOD, Northwest Med. **23**:279 (June) 1924.

Trueblood reports a case in a child aged 10 weeks, in which vomiting began at the age of 2 weeks. Suspecting pyloric stenosis the child was fed a thick cereal gruel without improvement and with a gradually increasing emaciation. The abdomen was enormously distended and showed marked peristalsis in the left lower quadrant and across the abdomen at the level of the umbilicus. Enemas yielded poor results and failed to reduce the distention. Roentgen-ray examination showed an enormously enlarged colon and a widely patent pylorus with a sigmoid lying to the right of the midline. Appendicostomy was performed and at operation the walls of the colon were found to be thick, stiff, vascular and with active peristalsis. The patient showed improvement for a week following operation, but contracted a respiratory infection which progressed to a fatal bronchopneumonia. Trueblood points out the poor prognosis in these patients because of the prolonged low grade toxemia and the malnutrition which is present.

SCOTT, Philadelphia.

REMARKS ON THE DIAGNOSIS AND TREATMENT OF CHRONIC INTUSSUSCEPTION. AMBROSE W. OWEN, Brit. M. J. **1**:904, 1924.

By chronic is meant those cases in which the intussusception is present for many days or even weeks without producing any acute obstruction. The author quotes Still's excellent description of the condition.

The diagnosis is made by feeling the sausage-shaped tumor, which varies in consistency under the fingers at different times, and by the sense of unnatural emptiness in the right iliac fossa. Roentgen-ray examination is no help. In some instances blood has been present at varying stages in the stool, and many cases have been diagnosed as tuberculous peritonitis. The symptoms in some cases have resembled "bilious attacks." Many patients have had symptoms for weeks and in one instance these symptoms lasted for five months. Recurrence is rare and the author does not believe pleating necessary; most patients recover with operation; in other words, the recovery depends on the diagnosis.

BROWN, Toronto.

Nervous Diseases

GANGLIONEUROMA OF THE CERVICAL AND THORACIC SYMPATHETIC GANGLIONS. D. P. STOUT, J. A. M. A. **82**:1770, 1924.

Stout reports two cases of ganglioneuroma that came under his observation, and reviews six other cases that have been reported.

A ganglioneuroma is a rare type of neoplasm composed chiefly of adult sympathetic ganglion cells, enormous numbers of neurofibrils, usually without any myelinated sheath and connective tissue. The ganglion cells, which multiply amitotically, are sometimes small with a single nucleus and at other times large with several nuclei, which are supposed to be degeneration forms. The nerve fibrils are usually naked axons, although in some cases reported the fibrils have

been myelinated. The fibrils are always in much greater number than could be supposed to have come from the number of ganglion cells found at the time of examination.

Grossly the tumors are usually firm, fibrous and circumscribed, and definitely encapsulated. The surface made by cutting often has a pale yellowish tint; occasionally there are red places and places of degeneration. Metastases are uncommon.

LOCALIZATION OF SPINAL BLOCK BY MEANS OF IODIZED OIL. ETHEL C. RUSSEL, J. A. M. A. **82**:1775, 1924.

A case is reported in which a spinal cord tumor was localized through the introduction of iodized oil into the cisterna magna. The oil being heavier than the spinal fluid, tends to seek the lowest level. If there is any obstruction in the spinal canal it may be located by a roentgen-ray picture.

The method is not without danger and is only recommended in selected cases where other means of localization have failed.

HENN, Chicago.

TETANY IN A BREAST-FED BABY WITH A DECIDED INCREASE IN CONVULSIONS AFTER RECEIVING SALINE HYPODERMOCLYSIS. CHARLES E. CONRAD, Southern M. J. **17**:477, 1924.

The author reports the case of a breast-fed baby who had severe convulsive seizures after having received a saline hypodermoclysis. The infant was aged 14 months, and exclusively breast-fed. There was no history of convulsions in the antecedents or any of the other children.

Three days preceding the giving of the hypodermoclysis the child had severe convulsions occurring from every ten to twenty minutes and lasting for forty-eight hours. They were controlled by heavy dosage of sodium bromid. At examination many of the characteristic phenomena of spasmophilia were found including laryngospasm and carpopedal spasm.

One week after cessation of the convulsions a normal saline hypodermoclysis was given for severe dehydration. One hour afterward severe convulsions began. After a second hypodermoclysis these became practically continuous. They were controlled under calcium bromid and morphin therapy, and the patient showed definite and apparently permanent recovery after weaning and a change to solid food with some cow's milk.

SCHLUTZ, Minneapolis.

THE RELATION BETWEEN INFANTILE CONVULSIONS AND THE CHRONIC CONVULSIVE DISORDERS OF LATER LIFE. DOUGLAS A. THOM, Arch. Neurol. & Psychiat. **2**:664, 1924.

Thom collected the histories of 111 patients who had convulsions prior to the age of 4, in which the convulsions were not associated with any acute or chronic cerebral condition. These cases were those in which the convulsions were associated with gastro-intestinal disturbances, acute infections, spasmophilia, pertussis, rickets and eleven without associated symptoms.

In order to ascertain the importance of such cases he studied their subsequent history. Sixty-two or 56 per cent. resulted in probable brain injury as evidenced by epilepsy, mental deficiency or death at the time of the convulsions. Forty-four per cent. showed no evidences of brain damage, although nineteen of the forty-nine cases were not in the best of health.

The author also cites two cases of convulsions associated with meningitis and encephalitis in which, following the recovery from these disorders, the children remained perfectly well. He suggests that the type of person who has convulsions associated with comparatively mild toxemias, is one in which the nervous system is unstable and more apt to have nervous manifestations later.

AVERY, Chicago.

PATHOGENESIS AND THERAPY OF TETANY. PART II. EXPERIMENTS WITH HYDROCHLORIC ACID MILK. KURT SCHEER; FRITZ MÜLLER and ADOLF SALOMON, Jahrb. f. Kinderh. **106**:85, 1924.

To make a liter of the hydrochloric acid milk, the authors use 600 c.c. of whole milk and 400 c.c. of a tenth normal solution of hydrochloric acid. The acid is added drop by drop after the milk has been boiled and cooled. Sugar is added to 5 per cent. Since the buffer value of cow's milk is much higher than of breast milk, the hydrochloric acid is added to relieve the stomach of the increased secretion required. The stool characteristics were not changed except in the direction of improvement in cases with frequent watery stools. This milk has a definite antispasmogenic action, improving the electrical irritability in spasmophilic infants.

The metabolism was studied over a control period of from two to four days, then from three to seven days of hydrochloric acid milk, then another control period of several days. There was a distinct decrease in alkali reserve, and an increased ammonia output in the urine during the period in which hydrochloric acid milk was fed. There was an increased output of phosphorus in the urine, with, however, a decreased output in the stool, so that the phosphorus balance remained positive. There was a distinct diuresis with the addition of hydrochloric acid.

The advisability of using an acidified milk, therefore, resolves itself into the question of general bodily metabolism as well as merely stomach acidity.

SUTHERLAND, Chicago.

Diseases of the Nose and Throat

ROENTGEN-RAY TREATMENT OF TONSILLAR AND ASSOCIATED LYMPHOID TISSUE. C. A. RUTHERFORD, Northwest Med. **23**:258 (June) 1924.

Rutherford cites four cases in which small repeated doses of roentgen ray, one twentieth to one fifth of a skin unit given at two weeks intervals, caused reduction in the size of the tonsils and amelioration of local and general symptoms. The conditions present were (1) recurrent tonsillitis with cervical adenitis, (2) chorea, (3) a nervous condition believed to originate in the thyroid, and (4) a case of chronic indigestion not improved by appendectomy. Rutherford reviews the work of a number of observers, experienced in the radiation of the faucial lymphoid tissues, and concludes that it is an efficient measure in treating inflammatory disease of these structures.

THE PRESENT STATUS OF ROENTGEN-RAY THERAPY FOR DISEASED TONSILS. O. M. ROTT, Northwest Med. **23**:260 (June) 1924.

Rott is skeptical of the value of roentgen rays in ridding the tonsil of pathogenic bacteria. He quotes observers who have found reduction of size accomplished in but a few cases. Likewise infectious organisms were removed in only a small number of cases. Many tonsils apparently reduced in size were later found to be filled with pus or cheesy débris. Until a less unpleasant method of eradicating these structures is found, reliance must be placed on surgery. Rott warns against delaying surgical removal in certain systemic conditions while awaiting possible improvement under radiation.

SCOTT, Philadelphia.

Diseases of the Skin

SEROLOGIC OBSERVATIONS ON EDEMATOUS CONDITIONS IN CHILDHOOD. B. LEICHENTRITT and HEDWIG ZWEIG, Jahrb. f. Kinderh. **106**:65, 1924.

Culture mediums containing serums of normal persons and of those suffering with edema of different types were prepared. Diphtheria bacilli were grown in these mediums and examined on the following day. A special type of

degeneration form which was considered edematous was studied particularly. These forms occurred most in mediums prepared with the serums of patients having edema due to severe nutritional disturbances, also to some extent in tuberculous cases with edema. The authors suggest that this edema may be due to lack of vitamin in the culture medium, and therefore also in the serums used. These edematous forms were less frequent or absent when the serums of normal cardiac and nephritic patients were used.

SUTHERLAND, Chicago.

THE ROENTGEN RAY IN THE TREATMENT OF CARBUNCLES AND OTHER INFECTIONS. FRED M. HODGES, Am. J. Roentgenol. **2**:442 (May) 1924.

Review of the literature shows that the treatment of carbuncles consists of leukodescent light, collodion painting, vaccine, zinc ionization, various cleansing lotions, crucial incision, excision and extensive cauterization and only little mention made of roentgen treatment. The radical surgical treatment is followed by marked scarring and deformity.

In a large series of cases, the technic consisted of 4 ma., 9 inch spark gap, 8 minutes with 9 mm. of aluminum, 9 inch distance, and half this dose repeated on the fourth day if necessary. The area treated included at least 1 inch of surrounding healthy tissue. A small incision was made as soon as the indurated part showed softening. The discharging sinuses were dressed daily with no medication.

The most marked effect was probably the rapid disappearance of pain. The following conclusions were drawn: (1) roentgen treatment should be given as soon as diagnosis of carbuncle is made; (2) a small incision should be made when softening first occurs; (3) pain is greatly relieved in nearly all cases and entirely in many; (4) the infection is usually limited and the duration of the disease shortened; (5) little scarring follows and there is no danger or pain associated with the radiation itself; (6) other localized infections of the skin and subcutaneous tissues respond very similarly to the roentgen ray, and (7) areas of lymphangitis usually disappear a few hours after the treatment.

The author believes that the treatment may be of value in erysipelas. The cases other than carbuncle treated with good results were stone bruises, palmar abscess and ischiorectal abscess. No effect was noted in subdeltoid bursitis, and in a case of an axillary carbuncle in which the pain was so great that the arm could not be lifted to expose the axilla.

STULIK, Chicago.

Surgery and Orthopedics

OSTEOMYELITIS OF THE ILIUM IN CHILDREN. CARL BEARSE, Boston M. & S. J. **190**:883 (May 22) 1924.

Differential diagnosis from tubercular hip important. Greatest point of tenderness usually posterior to great trochanter. In chronic cases roentgen ray is a decided help but in acute cases may show nothing. Since the ilium is a flat bone with a thin cortex early perforation is common. Prognosis is grave because of proximity to the hip joint and peritoneal cavity.

GENGENBACH, Denver.

ACUTE APPENDICITIS IN CHILDREN. G. P. MULLER and I. S. RAVDIN, J. A. M. A. **82**:1853, 1924.

This paper is based on an analysis of fifty-eight cases of acute appendicitis. Diagnosis is complicated because the classical symptoms of pain, nausea, vomiting, tenderness, rigidity and elevation of temperature may be observed in children who are not suffering from appendicitis.

Pain, an invariable symptom, is at first referred to the umbilicus. The spreading of inflammation to contiguous structures leads to secondary pain at site of the appendix. Sudden relief of pain usually is significant of perforation or gangrene.

Tenderness is difficult to interpret in the fretful child and is apt to be deceiving in that it is more often exaggerated than underestimated. Rigidity of involuntary type is extremely important and often depends on amount and location of peritoneal extension.

The average white cell count was 16,920 cells per centimeter, with polymorphonuclear leukocytes ranging from 80 to 96 per cent. Nausea and vomiting are not to be relied on in children under the age of puberty.

In diagnosis a thorough lung examination is necessary. Pneumonia, pyelitis, Pott's disease, gastro-enteritis, fecal impaction, and intestinal obstruction must be considered. Rectal examination is very important since the pelvis is shallow and the cecum lies low in the pelvis. Urinary symptoms may predominate, owing to proximity of the appendix to the bladder wall.

The authors' youngest patient was aged 4 years. They believe the cases increase with age. Prognosis is good if diagnosis is made early and operation occurs before inflammation has spread too far. Children do poorly under expectant treatment. The administration of purgatives before diagnosis has been established is the cause of much harm. If necessary to obtain an evacuation of the bowels, adequate results may be received through an administration of enemas.

HENN, Chicago.

Miscellaneous

SUDDEN DEATH IN CHILDHOOD. RUDOLPH BREZIK, Bratislava Med. J. **3**:244 (Jan.) 1924.

Brezik gives the causes of sudden death as upper respiratory infections in marasmic children; acute gastro-intestinal diseases including aspiration of regurgitated material; acute infections of the central nervous system; post infectious toxemia; and status thymicolymphaticus.

He reports the case of a boy, aged 8 years, with nocturnal enuresis who had no enuresis after weak faradic current application over the bladder. After several months a second treatment was attempted and the boy cried and fought as at the first treatment. Suddenly he became limp and died, in spite of artificial respiration, intravenous epinephrin, cardiac massage and intrapericardial strophanthin. Past history: dry pleurisy in 1920, tonsillectomy in 1921, chickenpox in 1922. Necropsy disclosed a simple struma. The thymus measured 9 by 11 cm. and varied in thickness from 0.1 to 1 cm., extending over half of the pericardium and into the muscles of the neck; the peribronchial glands were calcified; there was hyperplasia of the lymph glands including Peyer's patches; traces of old pleuritis; hemorrhagic patches in pleura and myocardium and right cardiac dilatation. The thymic gland weighed 56 gm. Diagnosis: Status thymicolymphaticus, myocarditis.

Chiari reported a thymus weighing 55 gm. in a boy, aged 11, and one weighing 50 gm. in a soldier, aged 23, who died while boxing. The right cardiac dilatation has often been reported.

The various theories cited include the toxic, the hypoplasia of chromaffin tissue, heart muscle changes and associated congenital developmental defects.

STULIK, Chicago.

THYROID SURVEY OF 47,493 CHILDREN IN CINCINNATI. ROBERT OLESEN, Pub. Health Reports, Vol. 39, No. 30, July 1924, U. S. Pub. H. S.

The survey was made in the elementary schools, and covered the age period from 6 to 17 years. Measurements of the neck were not considered as satisfactory as palpation, so thyroid enlargements were classified as "very slight," "slight,"

"moderate," "marked," "very marked," and adenoma. Of the boys, 26.6 per cent. had enlarged thyroids and 39.8 per cent. of the girls, or 33.2 per cent. in all. The greatest prevalence is between 11 and 13 years of age. The moderate and marked enlargements were more frequent in girls. The incidence was practically the same in colored and white children. There was no difference noted in the mentality of goitrous and nongoitrous individuals.

The author recommends the use of iodized table salt for prophylaxis, though the survey does not include data on prophylaxis.

SUTHERLAND, Chicago.

LEAD POISONING IN CHILDREN WITH SPECIAL REFERENCE TO PICA. JOHN C. RUDDOCK, J. A. M. A. **82**:1682, 1924.

There are many ways in which lead may be introduced by way of the mouth including paint from toys, candies colored with lead chromate, in printer's type used as a plaything, lead oxid ointment, water or milk that has stood in lead receptacles, or in medication, e. g., lead acetate solution in treatment of poison oak, by sucking paint from the mother's face, by nursing after use of lead preparations on the breast, or by swallowing leaden objects, such as B.B. shot.

Two cases are reported in which both patients had gnawed the paint from furniture. In one, a boy, aged three years, there was a history of nervousness, irregular sleeping hours, abdominal cramps, loss of weight, appetite, listlessness, night cries, and progressive anemia; in the other there was an uncontrollable desire to chew any painted object, three series of convulsions, and a strabismus.

In lead poisoning there is often a history of pica, and finding the symptoms of irritability, loss of weight, poor appetite, foul breath, epigastric or leg pains, constipation, normal temperature usually, except in fatal cases, paralysis of cranial nerves; colic is more frequently observed than paralysis, convulsions are rather frequent, either local or general. Irritability, restlessness, and a blue line on the gums are common symptoms. The blood picture, except for a secondary anemia, usually tells little unless the disease has been present for a long time. Direct evidence of lead poisoning is obtained through the finding of lead in the urine or feces.

The cases have been divided by Turner into four groups:

1. Paralytic cases, showing wrist and foot drop, spasm of the calf muscles and as a secondary lesion, a persistent talipes equinus.
2. Cases characterized by pains in abdomen and limbs, habitual constipation, and occasionally a blue line on the gums.
3. Children suffering from ocular neuritis.
4. Eclamptic cases with severe and persistent convulsions which often end fatally.

Treatment may be considered from three points of view:

1. Prophylactic: careful supervision of children during the first three years, and warning the public through wide publicity.
2. Symphonatic.
3. Medicinal: in which an attempt is made to eliminate lead from the system by use of potassium iodid, from 3 to 5 grains, three times a day, with a morning purge of magnesium sulphate. Where feasible Gibson's two bath ionization system may be successful.

HENN, Chicago.

Book Reviews

EXAMINATION OF CHILDREN BY CLINICAL AND LABORATORY METHODS. By ABRAHAM LEVINSON. St. Louis, C. C. Mosby Company, pp. 146. $3.50.

As the author states, there is a growing need for a reference work on clinical and laboratory methods of examination of children. Some book conceived and written to meet this need will be most welcome to students, general practitioners and those especially interested in children.

The execution of this idea as expressed in the volume is good but shows certain points of weakness. In an effort to be complete in subject matter included, a certain amount of thoroughness has been sacrificed. In several instances this renders the value of the book somewhat doubtful. For example, the description of technic and discussion of the Schick test and toxin-antitoxin administration for diphtheria immunization does not correctly carry out the subject. A second serious weakness is noted in describing the symptoms and method of eliciting physical signs in children; there is more discussion of the disease which may be present than of the symptom or sign itself. A further weakness is the incompleteness of the various descriptive passages. This incompleteness is a source of annoyance, possibly even danger, since no one could apply the information in a practical and helpful way, and a medical student might well be confused. For example, in explanation of a photograph (Fig. 9, page 27) the text says "tuberculids accompany active tuberculosis. Tuberculids must be differentiated from lichen urticatus and from syphilitic papules."

The sections describing laboratory methods are complete but contribute little information of special value. After all, laboratory methods for children differ very little from those for adults. Certain conditions having a higher incidence in children may need more emphasis.

The book has a good form, is readable, well illustrated with nonessential photographs, charts and diagrams. On the whole the book falls short of fulfilling the existing need, and because of inaccuracy cannot be considered safe in the hands of inexperienced students.

LES ENFANTS NERVEUX. DIAGNOSTIC, PROGNOSTIC APTITUDES. By DR. ANDRÉ COLLIN. Paris, J. B. Balliere et Fils, 1924. 155 pages. Price, 6 francs.

In this volume an attempt is made to discuss abnormal children from a physiologic viewpoint. Dr. Collin lays particular stress on the differences of function of various parts of the nervous system. He stresses the fact that motor disturbances do not necessarily involve mental defects, and vice versa.

On the whole, the viewpoint is sound, and the author makes a very definite attempt to place the study of the neurologic disturbances of childhood on a simple and intelligible basis.

News and Comment

ITALIAN SOCIETY OF PEDIATRICS

The section on Pediatrics of the Italian Congress of Medicine will meet at Milan, Italy, Oct. 22-25, 1924.

The following program will be presented:

1. Determination of the Alimentary Need of the Infant, by Pestalzza Camillo, and Caffarena Dario.

2. Diatheses and Constitutions, by Berghinz Guido.

3. Parascholastic Institutions and their Hygienic and Social Importance, by Raspi Mario.

Society Transactions

AMERICAN PEDIATRIC SOCIETY

Thirty-Sixth Annual Meeting, Pittsfield, Mass., Fifth Session, June 5-7, 1924

D. M. Cowie, M.D., *in the Chair*

Experiments on the Action of Light in Relation to Rickets. Presented by Dr. Alfred F. Hess.

Radiation has acquired a new significance for physicians within the last few years, especially for those who are concerned with the welfare and treatment of infants. Although we all realize and recognize the value of light rays in the treatment of rickets and some other diseases, it is only too true that little or nothing is known regarding the action of these rays, and the mechanism by which they produce their remarkable effect. The experiments which I wish to communicate are novel and seemed of interest in this connection.

It occurred to us to ascertain whether the treatment of inert substances with ultra light rays could endow them with antirachitic properties. With this end in view we irradiated various fluids with the mercury vapor quartz lamp. To summarize the results of these experiments it may be stated that it was found that cotton seed oil when rayed for an hour at a distance of one foot had acquired antirachitic potency. The experiments were carried out as follows: A very thin layer of the oil was placed in a Petri dish and irradiated and then fed to young rats in amounts of 0.1 c.c. and 0.25 c.c. daily. The control animals received oil which had not been irradiated. The rickets-producing diet was the low phosphorus dietary (No. 84) with which we have fed many hundreds of rats in the course of the last few years, and the technic the same which has been followed throughout our work. Questioning whether the cotton seed oil in itself might be somewhat antirachitic, linseed oil was substituted and the experiment carried out in the same way, 0.1 c.c. and 0.25 c.c. being given daily to each rat. The same result was obtained, namely, the development of rickets with the nonirradiated oil and the prevention of rickets with the oil which had been irradiated.

Among experiments which failed may be mentioned the attempt to prevent rickets by means of fluids which contained radium. Water to which radium bromid had been added in very small amounts was fed daily but without any effect. This was true, likewise, in regard to linseed oil to which minimal amounts of radium had been added. Failure also resulted with subcutaneous injections of radium water.

In view of the fact that peroxid of hydrogen has been stated to be formed as the result of ultraviolet irradiation, a solution of this substance was fed to rats. However, neither 0.2 nor 0.5 per cent. of hydrogen peroxid conferred the slightest immunity. All these additions were fed separately by pipet and not incorporated in the diet.

As is well known, ozone is given off by the mercury lamp, especially during the initial period. It seemed, therefore, worth while to test its efficacy. Accordingly, water was ozonated by means of an ozonating machine and was immediately fed to a series of rats. It was found to possess no protective action whatsoever.

Mineral oil was irradiated in the same way as the other oils, but gave a negative result when fed in the same amounts.

We shall not attempt to explain these results by means of hypotheses. It may be stated, however, that the oil was found to have been changed but little

in its iodin number, that is to say, in its content of unsaturated fatty acid, although the total acidity was somewhat increased. The color was slightly bleached, as has been noted by others. Peculiarly enough it frequently acquired a somewhat fishy odor resembling that of cod liver oil. Naturally, one of the first things which suggests itself is the possible association of a phenomenon of this kind with vitamins. Whether experiments of this kind will be serviceable in furthering our knowledge regarding the formation of the antirachitic factor, or be of therapeutic value in increasing the potency of antirachitic substances, such as cod liver oil, must be ascertained by subsequent investigation. These are subjects which are occupying us at the present time.

DISCUSSION

DR. GERSTENBERGER: Did you use butter oil or any other substance, such as protein?

DR. HESS: I did not use butter oil. I do not think butter would be a very good substance to use as it has a variable antirachitic value. We used water first and then chose oil because we thought that there might be some physical effect apart from a chemical effect. I do not know whether there is anything in that idea. The radiated oil seemed to be much better than any other fluid. We used water and other substances. Why do you suggest butter?

DR. GERSTENBERGER: To increase the antirachitic value of the butter oil.

DR. HESS: I used two kinds of cod liver oil, one eight or ten times stronger than the other, in order to see whether irradiation would intensify the antirachitic properties of the weaker oil to the same extent that it did those of the stronger oil. We allowed the oil to remain in storage twenty days.

THE EFFECT OF THE ROUTINE ADMINISTRATION OF COD LIVER OIL ON THE DEVELOPMENT OF RICKETS IN THE BREAST FED. Presented by DR. L. R. DEBUYS.

This study was conducted precisely the same way as the previous one. It covered a period of twelve consecutive calender months. Only breast fed babies were studied. There was a greater percentage of mothers who nursed their babies exclusively than in the previous study. The diets of the mothers were not restricted. Hygienic measures were advised. There were 198 infants included in the study, 72 white and 119 colored. The meteorologic summary was studied, as were also the individual symptoms, and the effect on nutrition, growth, and development. The summary is as follows:

1. The clinical symptoms usually ascribed to rickets, namely, cranial bosses, costal beading, epiphyseal enlargement, flaring ribs, and craniotabes, formed the basis of this study.

2. Cranial bosses was the most frequent symptom recorded, costal beading, epiphyseal enlargement, flaring ribs and craniotabes followed in the order named.

3. These symptoms developed in spite of the administration of an emulsion of pure Norwegian cod liver oil in doses of one-half teaspoonful given three times a day.

4. The average intensity of each of these clinical symptoms was greater than in the previous study, when cod liver oil was not administered, with the exception of epiphyseal enlargement and costal beading. In each of these two symptoms the average intensity was less in this study.

5. All the symptoms began earlier in this study than in the previous one. It is of interest to note that in the first three months of this study there were 89 hours less of actual sunshine and an average of 8.3 per cent. less possible sunshine per month than for the same period in the previous study.

6. The meteorologic summary for the period of this study showed the percentage of possible sunshine to be 2 degrees above the normal average. It was, however, 1.9 degrees less than for the period of the previous study. The precipitation for the period of this study was 6.28 inches above the normal and 10.91 inches more than the precipitation for the period of the previous study. The atmospheric pressure, temperature and humidity were about the same as for the previous study.

7. The seasonal peak for the combined symptoms of the disease was noted in the month of July, the greatest height being July 26.

8. The seasonal peak for this study differed from the peak of the previous study which occurred in the month of March.

9. During the month of July and August the percentage of possible sunshine was at its minimum for the period of this study. The precipitation for these months was more than for any two consecutive months in the study.

10. The increase in the precipitation for July, 1923, over July, 1922, was greater than the increase of precipitation for March, 1922, over March, 1923.

11. The total number of hours of actual sunshine for the period of this study was 116.8 less than for the period of the previous study.

CONCLUSIONS

Considering rickets from the clinical symptoms ascribed to it which occur within the first year of life and which formed the basis of this study the disease was more marked during the period of this study when cod liver oil was given. It may be that the amount of cod liver oil was insufficient as a preventive or that the cod liver oil was greatly deficient in the essential antirachitic factors, or that the adverse meteorologic phenomena were such as to offset the beneficial effects of the cod liver oil, or that the clinical symptoms ascribed to rickets may not be due exclusively to rickets, or that there may very likely be some other influencing factor or factors.

Considering rickets from the clinical symptoms of enlarged epiphyses and costal beading, the disease was beneficially influenced by the routine administration of cod liver oil in spite of the adverse meterologic conditions. Considered from all the clinical symptoms, sunshine and precipitation seemed to have their influence on the severity of the rickets.

DISCUSSION

DR. FINDLAY: My experience with cod liver oil is chiefly as a therapeutic agent and not as a prophylactic. I would like to get, while this discussion is going on, your experience as to the therapeutic value of cod liver oil. In my experience, from the curative point of view, cod liver oil has been disappointing. At the present moment rickets is entirely gaged by the bone changes or the blood changes. I would suggest that we also take into consideration changes in the muscle tone. A most striking thing is to take two children both suffering from severe osseous changes; let one child run while the other does not and observe the difference in these two children. I am not speaking against cod liver oil, but let us compare the effects of cod liver oil with those of exercise. Take a child with rickets, one who is able to walk and allow him to run about. Then take another child in the hospital on 4, 5 or 6 ounces of cod liver oil daily, and at the end of a certain period of time you will not see as much improvement in the ability of this child to run as you will see in the first child, even though the cod liver oil may produce a greater effect on the ossification than is seen in the child who is exercising. With exercise, there will be an increase in ossification but not so marked as with cod liver oil, but, on the other hand, cod liver oil has little effect on the muscular tone, while exercise has the greatest effect, so we are not as enthusiastic over cod liver oil in rickets as you are.

The question is whether cod liver oil is going to help in regard to the etiology of the disease. With reference to the use of cod liver oil as a prophylactic, I would say in the first place, cod liver oil is not a natural food for infants. In the second place we use quinin as a prophylactic and a curative agent in malaria, but no one would suggest that the absence of the quinin is the cause of malaria. That is a parallel to the assumption made in regard to cod liver oil. This work of Dr. Hess' makes the question more confused than ever. The fact I want to have you appreciate is that because we are applying cod liver oil as a prophylactic, we should not assume that we are giving the antirachitic factor. It is not in the nature of a vitamin at all; it is quite different from the other factors. It acts in only one way. It does not act when given subcutaneously or in any other way. We have tried and it has not the slightest effect. It only acts when given by the intestine on some disease in the intestine which is hindering the absorption of calcium. I have heard at this meeting a most illuminating contribution on the acid base balance, which showed of what tremendous importance these things are and that some little substance in the intestines may be upsetting the balance and interfering with absorption.

I should like to take this opportunity of expressing my thanks for your invitation to come to this meeting, and for the great benefits that I have obtained.

OBSERVATIONS ON CELIAC DISEASE. Presented by DR. CHARLES GILMORE KERLEY and DR. HOWARD CRAIG (by invitation).

The material on which this study is based includes eighteen cases seen since 1920 and brought to a conclusion, and three additional cases under treatment at the present time. When a physician assumes the care of a patient of this kind, he should tell the parents that no results should be expected at once; unless this is done, the parents are likely to become discouraged and to take the child to another physician. A formula which we have found to be a great help in these cases, is one consisting of 5 per cent. casein, 5 per cent. lactose, and 5 per cent. starch. In the preparation of this food, the casein is boiled in the presence of the starch. The casein is insoluble in the starch, but in this medium it is held in fine suspension. If the child is 20 months old, it may have scraped beef and egg yolk four or five times daily and dry bread. Usually two or three bananas are given daily; they are prepared by rubbing them through a sieve and then beating the pulp until it is light like mayonnaise. Children will often take bananas prepared in this way when they will take no other food. The banana pulp is sometimes thickened with gelatin. Other foods that are allowed are the white meat of chicken, rare steak and a certain amount of bread stuff and roughage. This is not an infallible method of feeding this type of patient, but it frequently yields excellent results. One important point to be emphasized is that the parents should be instructed not to worry about the stools.

DISCUSSION

DR. HEIMAN: Has Dr. Kerley tried transfusion? That is also a very helpful agent, especially if there is marked anemia.

DR. KERLEY: Yes, I used transfusion about four weeks ago in a child, aged 4 years, without benefit.

DR. MILLER: Have you used rice jelly? I have found it well borne in these cases.

DR. KERLEY: Rice jelly has not appeared to be of greater value than other cereals.

DR. CHARLES HENDEE SMITH: I think Dr. Sidney Haas' suggestion of giving banana should be mentioned. He gives sour milk and banana, the last thing in the world one would think would work. I have recently treated three babies with celiac disease, and the banana was the only form of carbohydrate that they could take.

DR. HERRMAN: In a certain number of cases the banana acts very well. It is a question whether it is entirely the character of the carbohydrate that is the agent in effecting the improvement. It is not unlikely that the banana contains some essential substance just as the orange does. I also have had cures with the banana diet. I have seen marked improvement in two cases of the celiac disease following a transfusion. This may be largely due to the hormones which the blood contains.

DR. HEIMAN: I have seen a favorable change take place by the use of the banana diet. It is a question whether it is not a hormone that is responsible for the beneficial results. It may be that, like orange, it contains certain necessary constituents. It is not a new treatment; it has been used before.

DR. MILLER: Banana was used by Dr. Vipond of Montreal. The banana contains a considerable quantity of tannin in addition to the carbohydrate. Dr. Vipond attributed its good effects to the astringent and to the carbohydrate. I have not been successful with it in simple diarrhea; I have not used it in celiac cases.

DEHYDRATION IN THE NUTRITIONAL DISORDERS OF INFANCY. A CORRELATION OF CLINICAL AND LABORATORY FINDINGS. Presented by DR. A. GRAEME MITCHELL and DR. LEON JONAS (by invitation).

Dehydration occurs frequently in infants suffering from those acute gastro-intestinal disturbances that are accompanied by diarrhea of a severe nature and not uncommonly by vomiting. Certain quite characteristic symptoms follow when fluid is not supplied or retained to make up for the water lost from the body. Almost any condition in which fluid is taken in insufficient amounts or is lost from the body will lead to somewhat similar manifestations. To be mentioned in this connection are the acute infections of the respiratory tract, intestinal obstruction and pyloric stenosis.

In summarizing the literature of studies made on infants in a dehydrated state it may be said that when loss of fluid from the body occurs as a result of diarrhea and vomiting, or when insufficient fluid is taken, dehydration of the tissues takes place. In certain dehydrated infants severe toxic symptoms may develop. Studies made when toxic symptoms are present demonstrate a retention of nonprotein nitrogen constituents of the blood and an acidosis. There is little kidney pathology in these cases. The explanation has been offered that both the acidosis and the retention in the blood of nonprotein nitrogenous waste products are due to the same cause: functional failure of the kidney due to lack of waste.

Our own studies which were made on thirty-five infants, all of whom showed clinical evidence of dehydration, lead us to the following conclusions: In infants who had clinical evidence of dehydration the determination of the blood urea nitrogen, uric acid and the carbon dioxid capacity of the blood plasma showed different values depending on whether or not the infants were suffering from toxic symptoms and hyperpnea.

If no toxic symptoms were observed in the blood, nonprotein nitrogen constituents were practically normal. If moderate toxic symptoms were present there usually was a moderate increase of nonprotein constituents, but if the patient showed distinct evidence of toxic symptoms the blood urea nitrogen and uric acid usually were decidedly increased over normal, but the increase was neither consistent enough nor great enough to indicate that uremia was a primary cause of the fatal termination.

A decrease in the carbon dioxid capacity of the blood plasma was found when the dehydrated infants showed clinical evidence of hyperpnea. In other infants in whom hyperpnea was not noticeable, but who were moderately toxic and whose blood usually contained an increase in nonprotein nitrogen constituents, the plasma showed a diminished carbon dioxid capacity in some instances. Usually, however, the carbon dioxid capacity of the plasma was normal when there was no increase in the respiratory rate and depth.

The p_H of the blood plasma was normal in 5 dehydrated infants, who did not show a decrease in the carbon dioxid capacity of the blood plasma. In one severely toxic infant with hyperpnea the p_H was within normal limits.

The results of the study of the p_H and the carbon dioxid of the plasma would indicate that the acid base balance was usually greatly diminished before death. However, since in several infants this did not occur and since in several with equally low acid base balance recovery followed, it would seem that the acidosis is an accompanying phenomenon and not a primary cause of either the condition or its fatal termination.

The phenolsulphonephthalein elimination by the kidney corresponded to the severity of the toxic symptoms.

Histologic examination of the kidneys of 10 infants who came to necropsy showed little evidence of pathology. This would furnish additional proof that the retention of blood urea nitrogen and uric acid was not due to nephritis, but apparently to dehydration per se.

DISCUSSION

DR. SCHLUTZ: These observations in an experimental way show many things that one would expect to find in a condition so acute if it is viewed from the physiologic standpoint. The whole process is one of acute concentration, not only involving the body fluids, but there is a concomitant concentration of the toxins of intermediate metabolism. The entire acid base balance one would expect to be out of equilibrium and in the direction of the acid phase, and some of the experimental data bear out this idea.

The necropsy findings are of interest, and again prove what we would expect to find, namely, that the changes found are apparently due to loss of water. This would also explain the difference in the nitrogen balance, the nonprotein constituents being practically normal if there were no toxic symptoms, while the nonprotein nitrogen was distinctly increased in the presence of toxins, showing that there was actual tissue destruction. Dr. Talbot's paper has a bearing on this subject, especially with reference to the effect of the presence or absence of water on the rapidity of the development of acidosis and hypoglycemia. I think his paper explains in a definite way some of the phenomena reported here this evening.

DR. TALBOT: I noticed in Dr. Mitchell's paper that there was an increase of uric acid in the blood. Possibly the explanation of that may be found in some of the fasting children which we are reporting, in whom we found quite regularly an increase in the blood uric acid. We cannot yet determine whether that is an actual increase, or whether it was due to some fault in technic involving the ketone bodies or other substances not yet tested. I think the subject of dehydration, however, is very important from the clinical point of view. I remember very clearly a case we had about two months ago. A child, aged 2 years, came into the hospital with vomiting and diarrhea. There was no acidosis but the child was markedly dehydrated and extremely ill and was calling constantly for water. Before the anhydremia was compensated 120 ounces of water were administered either by mouth, rectum or subcutaneously. Anyone studying the question of dehydration should take into consideration the fact that the normal water intake is 48 ounces in twenty-four hours; if the child does not get the 48 ounces of water that amount should be made up later. If there is any fever the child loses more water on account of the increased metabolism, and if there is diarrhea there is a loss of still more water. I think this should be considered because in dehydration tremendous amounts of water are required to save the child.

DR. HOWLAND: It is important that we should recognize that the loss of water and the diminution of the plasma bicarbonate are secondary phenomena. We should not be content with believing that the problem is solved when we recognize these phenomena, important as they may be. The process that causes them is still undetermined.

DR. MITCHELL (in closing): These studies simply emphasize again what was brought out this morning, namely, the importance of keeping up the fluid intake. We made the attempt to study and plot charts to see whether we could get any changes in the blood chemistry relative to the fluid intake and the fluid loss but the number of cases was to small to show anything definite.

OBSERVATIONS ON THE ACTION OF ACID-PRODUCING SUBSTANCES IN NEPHRITIS.* Presented by DRS. KENNETH D. BLACKFAN and BENGT HAMILTON (by invitation).

Data were presented showing that when calcium chlorid or magnesium sulphate is given to patients with nephritis and edema, the diuretic action of these salts occurs in the presence of an increased acidity of the blood plasma: also that an identical increase in plasma acidity occurs when ammonium chlorid or ammonium sulphate is given. The inference was drawn from these data that the diuretic action of calcium chlorid or magnesium sulphate is in some way due to the acid effect of these salts, and that the basic radical (calcium or magnesium) plays no direct rôle in the removal of edema fluid.

This inference is opposed to the belief of Blum and Fischer. Blum has supposed that the diuretic action of calcium chlorid is due to the effect of the calcium ion. He assumes an antagonism between calcium and sodium in consequence of which, when the calcium intake is increased, sodium is driven out of the body, and with it goes a certain amount of edema fluid. Fischer, in explaining the diuretic action of the salts (calcium chlorid or magnesium sulphate) which we have studied, believes the basic radical, calcium or magnesium, to be the important factor. He thinks that they operate by overcoming an acidosis which he considers to be the underlying cause of the edema. Our explanation, that an increased acidity of the plasma brings about a removal of the edema fluid, is thus directly the opposite of Fischer.

Gamble and Ross, in their studies of the action of calcium chlorid and of ammonium chlorid in tetany, have shown that these two salts produce an effect consisting of an increased acidity of the plasma and a diuresis. It was this observation that led the writers to question the part played by the basic radical of these salts.

Charts were presented illustrating the two points which were emphasized, namely, that the diuretic action of calcium chlorid and magnesium sulphate is accompanied by an increased acidity of the plasma and that both of these effects can be obtained by giving ammonium chlorid or ammonium sulphate. This led the writers to believe the basic radicals, calcium and magnesium, bear no discernible relation with the diuretic action of these acid producing salts.

SUMMARY

1. The administration of calcium and ammonium chlorid and magnesium and ammonium sulphate is followed by a diuresis and an acidosis (change in the plasma bicarbonate and the hydrogen-ion concentration of the blood).

2. The diuretic action of these salts is due to their acid effect and not to the basic radical (calcium and magnesium and ammonium).

3. The diuretic action, while only temporary, is of therapeutic value in the treatment of nephritic patients with edema, probably also in selected patients with cardiac edema.

4. Ammonium sulphate is more palatable than any of the other salts, and it does not exert the cathartic action of magnesium sulphate.

5. Care needs to be exerted in the administration of these salts on account of the acidosis which they induce.

6. It is of interest that a different salt or a combination of salts may induce diuresis when one salt fails.

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A Study of the Effect of Acid-Producing Salts on Fixed Base Excretion in the Urine from the Point of View of the Manner of their Action in Removing in Edema Fluid.* Presented by Drs. James L. Gamble and Bengt Hamilton (by invitation).

Measurements of the increase in urine of chlorid, of ammonia and of total fixed base (determined by Fiske's method) following ingestion of calcium chlorid, show a large increase in chlorid, a much smaller increase in ammonia and an increase in fixed base agreeing approximately with the excess of the chlorid increase over that of ammonia. Measurements of calcium in the urine demonstrate that calcium constitutes only a very small part of the increased fixed base excretion. Ingestion of calcium chlorid is thus shown to produce a withdrawal of fixed base from the body, apparently in consequence of a deficient ammonia production. That this increase in fixed base excretion is not an effect of the ingested calcium was demonstrated by giving ammonia chlorid. Following ingestion of this salt the changes in the excretion of chlorid, of ammonia and of fixed base in urine were found to be identical with those caused by calcium chlorid. The effect of calcium chlorid or of ammonium chlorid was found to be much larger and was sustained over a larger period in the presence of edema than when the kidney function is normal.

Similarly, magnesium sulphate and ammonium sulphate were both found to produce a large increase in the excretion of the sulphate radical (SO_4), which was incompletely covered by an increase in ammonia, the deficit being represented by an increased excretion of fixed base, only a small part of which was magnesium. It was also noted that ingestion of the magnesium salts produces an increase in urine chlorid.

The change in the acid base structure of the blood plasma causing the increased plasma acidity which follows ingestion of these acid producing salts was found to be due to an increase in plasma chlorid which, total fixed base in the plasma being maintained at closely its usual value, reduces proportionately the plasma bicarbonate. This event might be expected following ingestion of these chlorids, which from the point of view of acid base metabolism are in effect hydrochloric acid, but is a rather surprising consequence of the increased metabolism of sulphuric acid, produced by giving magnesium or ammonium sulphate. Following ingestion of the sulphates, the very small concentration at which sulphate is normally carried was found to be not appreciably increased. Chlorid however, was increased to about the same extent as when calcium or ammonium chlorid were given. The total fixed base of the plasma was found to remain at closely its normal value in spite of the large withdrawl of fixed base in the urine, caused by these acid producing salts. This is regarded as indicating that the increased excretion of fixed base is accompanied or at least closely followed by secretion of a corresponding amount of body water.

DISCUSSION

Dr. Talbot: I think this work is extremely important. I was much impressed with the method of presentation which makes comparisons possible. Dr. Gamble has calculated everything as one-tenth normal acid or alkali which brings out many factors in reference to the acid base equilibrium that we have overlooked in the past. What is shown in the blood chemistry is that the amount of total base is not changed when the body edema is lost. This is a very significant fact. From the practical point of view I feel indebted to Drs. Blackfan and Gamble for this work which has helped me in some cases during the last year.

Dr. Cowie: This is a very valuable piece of work. It is important to differentiate the type of nephritis one may be dealing with. Both nephritis

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and nephrosis produce edema. I should like to ask what criteria were used in arriving at the diagnosis of nephritis in these cases. Nephritis and nephrosis respond differently to treatment.

DR. BLACKFAN (in closing): I did not realize that you were asking me to differentiate between nephrosis and nephritis. In the first few charts the observations were made on patients we refer to as having nephrosis, and later the charts were those on patients whom we would not hesitate to speak of as having chronic nephritis. Yet from the standpoint of therapy, the reaction was the same. I am not in a position to discuss the various types of nephritis. I think that is a subject on which there is still much work to be done.

THE NORMAL KIDNEY: A FILTER FOR BACTERIA. Presented by Dr. HENRY F. HELMHOLZ.

This study of the permeability of the normal kidney was undertaken to determine whether bacteria were excreted in much the same manner as are urea, salts and water. In recent literature, numerous references have been made to the excretion of bacteria as a function of the normal kidney (Graves and Davidoff, J. Urol.) A great deal of experimental work has been done on the subject and conclusions diametrically opposed arrived at. The experiments of Biedl and Kraus are those that are practically always quoted when the secretion of bacteria by the normal kidney arises.

The work to be reported may be divided into four sections. First: the appearance of bacteria in the urine, in the blood stream, and in the kidney after intravenous injection. The animals were sacrificed at the end of ten minutes, one hour, four hours, seven hours, twenty-four hours, and forty-eight hours. The left kidney was incubated for twenty-four hours to determine, if possible, the number of bacteria present in the kidney substance. The right kidney was fixed immediately. Both virulent and avirulent *Staphylococcus aureus, Bacillus coli,* and *Streptococcus hemolyticus* and *viridans* were used in these experiments. At no time were bacteria found in the urine in four hours. After injection only virulent staphylococci were constantly found in the blood after seven hours. Second: The effect of diuresis on the excretion of bacteria. The experiments of Biedl and Kraus were conducted with the injection of sugar and saline solution intravenously in order to stimulate the diuresis.

In the first series of thirty-two experiments in which the *Staphylococcus aureus, Bacillus prodigious,* and colon bacillus were injected, there was only a single instance in which bacteria were found in the urine. The single experiment in which *Staphylococcus aureus* was found in the urine was negative in the plate in which 10 c.c. was used, negative in the plate in which 5 c.c. was used, and positive in the liquid culture in which 5 c.c. was used. All of the other experiments were negative.

In a second series of experiments with virulent *Bacillus coli,* virulent staphylococcus, and *Streptococcus lacticus,* an attempt was made to produce as great a flow of urine as possible. Diuresis, varying from 50 to 300 c.c. per kilogram per hour were reached. In only one experiment were there bacteria in the urine, and in this instance there was a large amount of blood found in the bladder. It is, therefore, evident that even with a tremendous output of urine, bacteria are not excreted through the normal kidney.

In order to check up on the work of Biedl and Kraus, thirteen experiments were done with the inlying catheter or repeated catheterization, giving small amounts of glucose intravenously. In twenty-four experiments in which the urine was obtained by catheter, twelve show positive cultures. In fifty-six experiments in which the urine was sterile in fifty-five instances, and in one single instance, there were bacteria present in one 5 c.c. specimen of urine, whereas 10 c.c. and 5 c.c. of the same specimen did not show bacteria. Our experiments demonstrate, thus, that technic very probably accounts for the presence of bacteria in the urine obtained by Biedl and Kraus, Roy and others.

Nineteen experiments were done in which the renal vein was clamped for intervals varying from one to sixty minutes. Bacteria were demonstrated in the urine in four animals, once after three minutes, twice after ten minutes and once after sixty minutes.

A similar series of eighteen experiments was done, clamping the renal artery and tying the ureter of the opposite side. Clamping the renal artery up to one hour did not interfere with the holding back of bacteria by the kidney.

Fourth, the urine obtained from the seventeen hydronephrotic kidneys showed no bacteria on culture. In a series of five experiments in which both ureters were tied, one experiment was positive.

A further change in the technic was used in that the right ureter was tied and the left ureter was clamped for periods of fifteen and sixty and 240 minutes. The clamp was then removed, bacteria injected, and the animal sacrificed from one to three and a half hours later. In any instance in which there was no blood in the urine were bacteria present.

CONCLUSIONS

The normal kidney filter does not permit bacteria injected intravenously to pass through the urine until local changes are produced. Diuresis of moderate and even extreme degree, produced by saline solution, glucose, or sucrose, does not increase the permeability of the kidney for bacteria. Clamping of the renal vein was the only condition which seemed to influence very definitely the permeability of the kidney. Tying of the renal artery up to one hour did not affect the permeability of the kidney for bacteria. In only one instance in which the hydronephrosis was produced were bacteria obtained from the urine of the hydronephrotic kidney. In a group of twenty experiments, blood was found in the urine on microscopic or macroscopic examination without finding bacteria in the urine on culture.